Avastin®

Bevacizumab

Antineoplastic agent

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Antineoplastic agent

ATC Code: L01F G01

1.2 Type of Dosage Form

Concentrate for solution for infusion.

1.3 Route of Administration

Clear to slightly opalescent, colourless to pale brown, sterile liquid for intravenous (i.v.) infusion.

Avastin is not formulated for intravitreal use (see section 2.4.1 General [2.4 Warnings and Precautions]).

1.4 Sterile / Radioactive Statement

Sterile.

1.5 Qualitative and Quantitative Composition

Active ingredient: Bevacizumab (humanised anti-VEGF monoclonal antibody).

Avastin is supplied in 100 mg and 400 mg preservative-free, single-use vials containing 4 ml or 16 ml of Avastin (25 mg/ml).

Each Avastin 100 mg vial contains 100 mg of bevacizumab.

Each Avastin 400 mg vial contains 400 mg of bevacizumab.

For excipients, As registered locally .

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Metastatic Colorectal Cancer (mCRC)

Avastin in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum.

Locally Recurrent or Metastatic Breast Cancer (mBC)

Avastin in combination with standard cytotoxic chemotherapy is indicated for first-line treatment of patients with locally recurrent or metastatic breast cancer.

Avastin in combination with taxanes, capecitabine or gemcitabine, is indicated for the treatment of patients with metastatic breast cancer after failure of first-line cytotoxic chemotherapy.

Advanced, Metastatic or Recurrent Non-Small Cell Lung Cancer (NSCLC)

Avastin, in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer.

Avastin, in combination with erlotinib, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations.

Advanced and/or Metastatic Renal Cell Cancer (mRCC)

Avastin in combination with interferon alfa-2a is indicated for first-line treatment of patients with advanced and/or metastatic renal cell cancer.

Malignant Glioma (WHO Grade IV) – Glioblastoma

Avastin in combination with radiotherapy and temozolomide is indicated for the treatment of adult patients with newly diagnosed glioblastoma.

Avastin, as a single agent, or in combination with irinotecan, is indicated for the treatment of patients with glioblastoma after relapse or disease progression.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Avastin, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Avastin, in combination with carboplatin and gemcitabine is indicated for the treatment of patients with recurrent, platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Avastin in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens.

Cervical Cancer

Avastin in combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for the treatment of persistent, recurrent, or metastatic carcinoma of the cervix.

2.2 Dosage and Administration

General

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

The safety and efficacy of alternating or switching between Avastin and products that are biosimilar but not deemed interchangeable have not been established. Therefore, the benefit-risk of alternating or switching need to be carefully considered.

Avastin should be prepared by a healthcare professional using an aseptic technique (see section 4.3 Special Instructions for Use, Handling and Disposal).

The initial Avastin dose should be delivered over 90 minutes as an i.v. infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Dose reduction of Avastin for adverse events is not recommended. If indicated, Avastin should either be permanently discontinued or temporarily suspended as described in section 2.4.1 General (2.4 Warnings and Precautions).

Avastin is not formulated for intravitreal use (see section 2.4.1 General [2.4 Warnings and Precautions]).

Metastatic Colorectal Cancer (mCRC)

The recommended dose of Avastin, administered as an i.v. infusion, is as follows:

First-line treatment:	5 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg of body weight given once every 3 weeks.
Second-line treatment:	5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks.

It is recommended that Avastin treatment be continued until progression of the underlying disease. Patients previously treated with Avastin can continue with Avastin treatment following first progression (see section 3.1.2, study ML18147).

Locally Recurrent or Metastatic Breast Cancer (mBC)

The recommended dose of Avastin is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an i.v. infusion.

It is recommended that Avastin treatment be continued until progression of the underlying disease.

Advanced, Metastatic or Recurrent Non-Small Cell Lung Cancer (NSCLC)

Avastin is administered in addition to platinum-based chemotherapy for up to 6 cycles of treatment followed by Avastin as a single agent until disease progression.

The recommended dose of Avastin when used in addition to cisplatin-based chemotherapy is 7.5 mg/kg of body weight given once every 3 weeks as an i.v. infusion.

The recommended dose of Avastin when used in addition to carboplatin-based chemotherapy is 15 mg/kg of body weight given once every 3 weeks as an i.v. infusion.

First-line treatment of NSCLC with EGFR activating mutations in combination with erlotinib.

The recommended dose of Avastin when used in addition to erlotinib is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

It is recommended that the treatment with Avastin in addition to erlotinib is continued until disease progression.

Please refer to the full prescribing information for erlotinib for patient selection and posology.

Advanced and/or Metastatic Renal Cell Cancer (mRCC)

The recommended dose of Avastin is 10 mg/kg of body weight given once every 2 weeks as an i.v. infusion.

It is recommended that Avastin treatment be continued until progression of the underlying disease.

Malignant Glioma (WHO Grade IV) – Glioblastoma

The recommended dose of Avastin, administered as an intravenous infusion, is as follows:

Newly diagnosed glioblastoma:	Avastin (10 mg/kg of body weight given once every 2 weeks) is administered in combination with temozolomide and radiotherapy for 6 weeks. Following a 4 week treatment break, Avastin (10 mg/kg of body weight given once every 2 weeks) is re-initiated in combination with temozolomide for up to 6 cycles of 4 week duration. After administration of up to 6 cycles of combined Avastin and temozolomide, Avastin (15 mg/kg of body weight given once every 3 weeks) is continued as a single agent until disease progression.
Treatment of recurrent disease:	10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks. It is recommended that Avastin treatment be continued until progression of the underlying disease.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

The recommended dose of Avastin administered as an intravenous infusion is as follows:

Front-line treatment:	When administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Avastin as single agent for 15 months or until disease progression, whichever occurs earlier.

Treatment of recurrent disease:	Platinum-sensitive: 15 mg/kg of body weight given once every 3 weeks when administered in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles followed by continued use of Avastin as single agent until disease progression Platinum-resistant: 10 mg/kg body weight given once every 2 weeks when administered in combination with one of the following agents – paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin (see section 3.1.2, study MO22224 for chemotherapy regimens). Alternatively, 15 mg/kg every 3 weeks when administered in combination with topotecan given on days 1–5 every 3 weeks (see section 3.1.2, study MO22224 for chemotherapy regimen). It is recommended that treatment be continued until disease progression.

Cervical Cancer

Avastin is administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan (see section 3.1.2 study GOG-0240 for further details on the chemotherapy regimens).

The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

It is recommended that Avastin treatment be continued until progression of the underlying disease.

2.2.1 Special Dosage Instructions

Pediatric Use: The safety and efficacy of Avastin in children and adolescents (<18 years) have not been established (see section 2.5.3 Pediatric Use [2.5 Use in Special Populations]).

Geriatric Use: No dose adjustment is required in patients ≥ 65 years of age.

Renal impairment: The safety and efficacy of Avastin have not been studied in patients with renal impairment.

Hepatic impairment: The safety and efficacy of Avastin have not been studied in patients with hepatic impairment.

2.3 Contraindications

Avastin is contraindicated in patients with known hypersensitivity to:

- Any components of the product

- Chinese hamster ovary cell products or other recombinant human or humanised antibodies.

2.4 Warnings and Precautions

2.4.1 General

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Gastrointestinal Perforations and Fistula

Patients may be at increased risk for the development of gastrointestinal (GI) perforation (see also section 2.6.1 Clinical Trials [2.6 Undesirable Effects]) and gallbladder perforation (see also section 2.6.2 Postmarketing Experience [2.6 Undesirable Effects]) when treated with Avastin. Avastin should be permanently discontinued in patients who develop gastrointestinal perforation. Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin may be at increased risk of fistulae between the vagina and any part of the GI tract (gastrointestinal-vaginal fistulae) (see section 2.6.1 Clinical Trials [2.6 Undesirable Effects], Gastrointestinal Perforation and Fistula).

Non-GI Fistula (see section 2.6.1 Clinical Trials [2.6 Undesirable Effects])

Patients may be at increased risk for the development of fistula when treated with Avastin (see section 2.6.1 Clinical Trials [2.6 Undesirable Effects]).

Permanently discontinue Avastin in patients with TE (tracheo-oesophageal) fistula or any Grade 4 fistula. Limited information is available on the continued use of Avastin in patients with other fistula. In cases of internal fistula not arising in the GI tract, discontinuation of Avastin should be considered.

Haemorrhage (see section 2.6.1 Clinical Trials [2.6 Undesirable Effects])

Patients treated with Avastin have an increased risk of haemorrhage, especially tumour-associated haemorrhage (see section 2.6.1 Clinical Trials [2.6 Undesirable Effects], Haemorrhage). Avastin should be permanently discontinued in patients who experience Grade 3 or 4 bleeding during Avastin therapy.

Patients with untreated central nervous system (CNS) metastases were routinely excluded from clinical trials with Avastin, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patients has not been prospectively evaluated in randomised clinical studies (see section 2.6.1 Clinical Trials [2.6 Undesirable Effects], Haemorrhage). Patients should be monitored for signs and symptoms of CNS bleeding, and Avastin treatment discontinued in the case of intracranial bleeding.

There is no information on the safety profile of Avastin in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting Avastin treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating Avastin therapy in these patients. However, patients who developed venous thrombosis while receiving Avastin

therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with full dose of warfarin and Avastin concomitantly.

Severe Eye Infections Following Compounding for Unapproved Intravitreal Use (see section 2.6.2 Post marketing Experience [2.6 Undesirable Effects])

Individual cases and clusters of serious ocular adverse events have been reported (including infectious endophthalmitis and other ocular inflammatory conditions) following unapproved intravitreal use of Avastin compounded from vials approved for i.v. administration in cancer patients. Some of these events have resulted in various degrees of visual loss, including permanent blindness.

Pulmonary Haemorrhage / Haemoptysis (see section 2.6.1 Clinical Trials [2.6 Undesirable Effects])

Patients with non-small cell lung cancer treated with Avastin may be at risk for serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis (see section 2.6.1 Clinical Trials [2.6 Undesirable Effects], Haemorrhage). Patients with recent pulmonary haemorrhage/haemoptysis (> ½ teaspoon red blood) should not be treated with Avastin.

Hypertension

An increased incidence of hypertension was observed in patients treated with Avastin. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting Avastin treatment. There is no information on the effect of Avastin in patients with uncontrolled hypertension at the time of initiating Avastin therapy. Monitoring of blood pressure is recommended during Avastin therapy (see section 2.6.1 Clinical Trials [2.6 Undesirable Effects]).

In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. Avastin should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy (see sections 2.6.1 Clinical Trials and 2.6.2 Postmarketing Experience [2.6 Undesirable Effects]).

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports of Avastin treated patients developing signs and symptoms that are consistent with posterior reversible encephalopathy syndrome (PRES), a rare neurological disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of Avastin. The safety of reinitiating Avastin therapy in patients previously experiencing PRES is not known (see sections 2.6.1 Clinical Trials and 2.6.2 Post Marketing [2.6 Undesirable Effects]).

Arterial Thromboembolism

In clinical trials, the incidence of arterial thromboembolic events including cerebrovascular accidents, transient ischaemic attack (TIA) and myocardial infarction (MI) was higher in patients receiving Avastin in combination with chemotherapy compared to those who received chemotherapy alone.

Avastin should be permanently discontinued in patients who develop arterial thromboembolic events.

Patients receiving Avastin plus chemotherapy with a history of arterial thromboembolism, diabetes or age greater than 65 years have an increased risk of developing arterial thromboembolic events during Avastin therapy. Caution should be taken when treating such patients with Avastin.

Venous Thromboembolism (see section 2.6.1 Clinical Trials [2.6 Undesirable Effects])

Patients may be at risk of developing venous thromboembolic events, including pulmonary embolism under Avastin treatment.

Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin may be at increased risk of venous thromboembolic events (see section 2.6.1 Clinical Trials [2.6 Undesirable Effects], Venous thromboembolism).

Avastin should be discontinued in patients with life-threatening (Grade 4) venous thromboembolic events, including pulmonary embolism. Patients with thromboembolic events ≤ Grade 3 need to be closely monitored.

Congestive Heart Failure (see section 2.6.1 Clinical Trials [2.6 Undesirable Effects])

Events consistent with congestive heart failure (CHF) were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation.

Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with Avastin.

Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.

In patients in study AVF3694g who received treatment with anthracyclines and who had not received anthracyclines before, no increased incidence of all-grade CHF was observed in the anthracycline + bevacizumab group compared to the treatment with anthracyclines only. CHF Grade 3 or higher events were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patients receiving chemotherapy alone. This is consistent with results in patients in other studies of metastatic breast cancer who did not receive concurrent anthracycline treatment (see section 2.6.1 Clinical Trials [2.6 Undesirable Effects]).

Neutropenia

Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus Avastin in comparison to chemotherapy alone.

Wound Healing

Avastin may adversely affect the wound-healing process. Serious wound healing complications with a fatal outcome have been reported.

Avastin therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experience wound-healing complications during Avastin treatment, Avastin should be withheld until the wound is fully healed. Avastin therapy should be withheld for elective surgery (see section 2.6.1 Clinical Trials [2.6 Undesirable Effects]).

Necrotizing fasciitis, including fatal cases, has rarely been reported in patients treated with Avastin, usually secondary to wound-healing complications, gastrointestinal perforation or fistula formation. Avastin therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated (see also section 2.6.2 Postmarketing Experience [2.6 Undesirable Effects]).

Proteinuria (see section 2.6.1 Clinical Trials [2.6 Undesirable Effects])

In clinical trials, the incidence of proteinuria was higher in patients receiving Avastin in combination with chemotherapy compared to those who received chemotherapy alone. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with Avastin. In the event of nephrotic syndrome, Avastin treatment should be permanently discontinued.

Hypersensitivity Reactions, anaphylactic reactions (including anaphylactic shock), Infusion relatedReactions(see section 2.6 Undesirable Effects, Clinical Trials and Postmarketing Experience)

Patients may be at risk of developing hypersensitivity reactions, anaphylactic reactions (including anaphylactic shock), and infusion-related reactions. Close observation of the patient during and following the administration of bevacizumab is recommended. . If an anaphylactic reaction occurs, the infusion should be permanently discontinued and appropriate medical therapies should be administered.

If an infusion-related reactions occurs, treatment should be temporarily interrupted until resolution of symptoms. Permanently discontinue Avastin for severe (Grade ≥3) infusion related-reaction. A systematic premedication is not warranted.

Ovarian Failure / Fertility (see sections 2.5.1 Females and Males of Reproductive [2.5 Use in Special Populations] and 2.6.1 Clinical Trials [2.6 Undesirable Effects])

Avastin may impair female fertility. Therefore fertility preservation strategies should be discussed with women of childbearing potential prior to starting treatment with Avastin

2.4.2 Drug Abuse and Dependence

Not applicable.

2.4.3 Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. However, there is no evidence that Avastin treatment results in an increase in adverse events that might lead to impairment of the ability to drive or operate machinery or impairment of mental ability.

2.5 Use in Special Populations

2.5.1 Females and Males of Reproductive Potential

Fertility

Avastin may impair female fertility. Women of child-bearing potential should be advised of fertility preservation strategies prior to starting treatment with Avastin. (see section 2.4.1 Warnings and Precautions, General and section 2.6.1 Undesirable Effects, Clinical Trials).

Repeat dose safety studies in animals have shown that bevacizumab may have an adverse effect on female fertility (see section 3.3.3 Impairment of Fertility). A substudy with 295 premenopausal women has shown a higher incidence of new cases of ovarian failure in the bevacizumab group compared to the control group. After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of patients. Long term effects of the treatment with bevacizumab on fertility are unknown.

Contraception

In women with childbearing potential, appropriate contraceptive measures should be used during Avastin therapy. Based on pharmacokinetic considerations, contraceptive measures should be used for at least 6 months following the last dose of Avastin.

2.5.2 Pregnancy

Angiogenesis has been shown to be critically important to foetal development. The inhibition of angiogenesis following administration of Avastin could result in an adverse outcome of pregnancy.

There are no adequate and well-controlled studies in pregnant women (see section 3.3.4 Reproductive Toxicity). [3.3 Preclinical Safety]). IgGs are known to cross the placental barrier, and Avastin may inhibit angiogenesis in the foetus. In the post-marketing setting, cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 2.6.2 Postmarketing Experience [2.6 Undesirable Effects]).

Therefore, Avastin should not be used during pregnancy.

Labour and Delivery

Not applicable.

2.5.3 Lactation

It is not known whether bevacizumab is excreted in human milk. As maternal IgG is excreted in milk and Avastin could harm infant growth and development, women should be advised to discontinue nursing during Avastin therapy and not to breast-feed for at least 6 months following the last dose of Avastin.

2.5.4 Paediatric Use

Avastin is not approved for use in patients under the age of 18 years. The safety and efficacy of Avastin in this population have not been established. Addition of Avastin to standard of care did not demonstrate clinical benefit in pediatric patients in two phase II clinical trials: one in pediatric high grade glioma and one in pediatric metastatic rhabdomyosarcoma or non-rhabdomyosarcoma soft tissue sarcoma. In published reports, cases of osteonecrosis at sites other than the jaw have been observed in patients under the age of 18 years exposed to Avastin (see see section 2.6.2 Postmarketing Experience and section 3.3.5 Other [3.3 Nonclinical Safety], Physeal Development).

2.5.5 Geriatric Use

Refer to section 2.4.1 General (2.4 Warnings and Precautions) under the subheading Arterial Thromboembolism.

2.5.6 Renal Impairment

The safety and efficacy of Avastin have not been studied in patients with renal impairment.

2.5.7 Hepatic Impairment

The safety and efficacy of Avastin have not been studied in patients with hepatic impairment.

2.6 Undesirable Effects

2.6.1 Clinical Trials

Summary of safety profile

Clinical trials have been conducted in patients with various malignancies treated with Avastin, predominantly in combination with chemotherapy. The safety profile from a clinical trial population of approximately 5500 patients is presented in this section. For post-marketing experience see section 2.6.2 Postmarketing Experience [2.6 Undesirable Effects. See section 3.1.2 Clinical / Efficacy Studies (3.1 Pharmacodynamic Properties) for details of major studies, including study designs and major efficacy results.

The most serious adverse drug reactions were:

- Gastrointestinal perforation (see section 2.4.1 General [2.4 Warnings and Precautions])
- Haemorrhage including pulmonary haemorrhage/haemoptysis, which is more common in NSCLC patients (see section 2.4.1 General [2.4 Warnings and Precautions])
- Arterial thromboembolism [see section 2.4.1 General (2.4 Warnings and Precautions)].

Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with Avastin therapy is likely to be dose-dependent.

The most frequently observed adverse drug reactions across clinical trials in patients receiving Avastin were hypertension, fatigue or asthenia, diarrhoea and abdominal pain.

Tabulated summary of adverse drug reactions from clinical trials

Table 1 lists adverse drug reactions associated with the use of Avastin in combination with different chemotherapy regimens in multiple indications, by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). These reactions had occurred either with at least a 2% difference compared to the control arm (NCI-CTC Grade 3–5 reactions) or with at least a 10% difference compared to the control arm (NCI-CTC [common toxicity criteria] Grade 1–5 reactions), in at least one of the major clinical trials. Adverse drug reactions are added to the appropriate category in the table below according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping adverse drug reactions are presented in order of decreasing seriousness. Some of the adverse reactions are reactions commonly seen with chemotherapy, however, Avastin may exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysaesthesia syndrome with pegylated liposomal doxorubicin or capecitabine, peripheral sensory neuropathy with paclitaxel or oxaliplatin, and nail disorders or alopecia with paclitaxel and paronychia with erlotinib

Table 1Very Common and Common Adverse Drug Reactions

System organ class (SOC)	**NCI-CTC Grade 3–5 reactions (≥2% difference between the study arms in at least one clinical trial)**		**All-grade reactions (≥10% difference between the study arms in at least one clinical trial)**
	Very common	**Common**	**Very common**
Infections and infestations		Sepsis Abscess Cellulitis Infection	
Blood and lymphatic system disorders	Febrile neutropenia Leucopenia Neutropenia Thrombocytopenia	Anaemia Lymphopenia	
Immune system disorders		Hypersensitivity, anaphylactic, infusion-related reactions	

Metabolism and nutrition disorders		Dehydration Hyponatraemia	Anorexia Hypomagnesaemia Hyponatraemia
Nervous system disorders	Peripheral sensory neuropathy	Cerebrovascular accident Syncope Somnolence Headache	Dysgeusia Headache Dysarthria
Eye disorders			Eye disorder Lacrimation increased
Cardiac disorders		Cardiac failure (congestive) Supraventricular tachycardia	
Vascular disorders	Hypertension	Thromboembolism (arterial) Deep vein thrombosis Haemorrhage	Hypertension
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism Dyspnoea Hypoxia Epistaxis	Dyspnoea Epistaxis Rhinitis Cough
Gastrointestinal disorders	Diarrhoea Nausea Vomiting Abdominal pain	Intestinal perforation Ileus Intestinal obstruction Recto-vaginal fistula** Gastrointestinal disorder Stomatitis Proctalgia	Constipation Stomatitis Rectal haemorrhage Diarrhoea
Endocrine disorders			Ovarian failure*
Skin and subcutaneous tissue disorders		Palmar-plantar erythrodysaesthesia syndrome	Exfoliative dermatitis Dry skin Skin discolouration
Musculoskeletal, connective tissue and bone disorders		Muscular weakness Myalgia Arthralgia Back pain Arthralgia	Arthralgia
Renal and urinary disorders		Proteinuria Urinary tract infection	Proteinuria
General disorders	Asthenia	Pain	Pyrexia

and administration site conditions	Fatigue	Lethargy Mucosal inflammation	Asthenia Pain Mucosal inflammation
Reproductive system and breast disorders		Pelvic pain	
Investigations			Weight decreased

* Based on a substudy from AVF3077s (NSABP C-08) with 295 patients

** Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category

Description of selected adverse drug reactions from clinical trials

The following adverse drug reactions, reported using NCI-CTC for assessment of toxicity, have been observed in patients treated with Avastin:

Gastrointestinal Perforation and Fistula (see section 2.4.1 General [2.4 Warnings and Precautions])

Avastin has been associated with serious cases of gastrointestinal perforation. Gastrointestinal perforations have been reported in clinical trials with an incidence of less than 1% in patients with metastatic breast cancer or non-squamous non-small cell lung cancer, up to 2% in patients with metastatic renal cell cancer, newly diagnosed glioblastoma, or ovarian cancer receiving front-line treatment, and up to 2.7% (including gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer. Cases of GI perforations have also been observed in patients with relapsed glioblastoma. From a clinical trial in patients with persistent, recurrent or metastatic cervical cancer (study GOG-0240), GI perforations (all-grade) were reported in 3.2% of patients, all of whom had a history of prior pelvic radiation.

The occurrence of those events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumour necrosis, diverticulitis or chemotherapy-associated colitis. A causal association of intra-abdominal inflammatory process and gastrointestinal perforation to Avastin has not been established.

Fatal outcome was reported in approximately a third of serious cases of gastrointestinal perforations, which represents between 0.2% and 1% of all Avastin treated patients.

In Avastin clinical trials, gastrointestinal fistulae (all-grade) have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer and ovarian cancer, but were also reported less commonly in patients with other types of cancer.

In a trial of patients with persistent, recurrent or metastatic cervical cancer, the incidence of GI-vaginal fistulae was 8.3% in Avastin treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. Patients who develop GI-vaginal fistulae may also have bowel obstructions and require surgical intervention as well as diverting ostomies.

Non-GI Fistula (see section 2.4.1 General [2.4 Warnings and Precautions])

Avastin use has been associated with serious cases of fistula including events resulting in death.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (GOG-240), 1.8% of Avastin treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vesical, or female genital tract fistulae.

Uncommon (≥0.1% – <1%) reports of fistulae that involve areas of the body other than the gastrointestinal tract (e.g. bronchopleural, biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience.

Events were reported at various time points during treatment ranging from 1 week to greater than 1 year from initiation of Avastin, with most events occurring within the first 6 months of therapy.

Haemorrhage

In clinical trials across all indications the overall incidence of NCI-CTC Grade 3–5 bleeding events ranged from 0.4% to 6.9% in Avastin treated patients, compared to 0 to 4.5% of patients in the chemotherapy control group. The haemorrhagic events that have been observed in Avastin clinical studies were predominantly tumour-associated haemorrhage (see below) and minor mucocutaneous haemorrhage (e.g. epistaxis).

- Tumour-associated haemorrhage

Major or massive pulmonary haemorrhage/haemoptysis has been observed primarily in studies in patients with non-small cell lung cancer (NSCLC). Possible risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, Avastin therapy, previous medical history of atherosclerosis, central tumour location and cavitation of tumours prior to or during therapy. The only variables that showed statistically significant correlations with bleeding were Avastin therapy and squamous cell histology. Patients with NSCLC of known squamous cell histology or mixed cell type with predominantly squamous cell histology were excluded from subsequent studies, while patients with unknown tumour histology were included.

In patients with NSCLC excluding predominantly squamous cell histology, all-grade events were seen with a frequency of up to 9% when treated with Avastin + chemotherapy compared with 5% in the patients treated with chemotherapy alone. Grade 3-5 events have been observed in up to 2.3% of patients treated with Avastin + chemotherapy as compared with <1% with chemotherapy alone. Major or massive pulmonary haemorrhage/haemoptysis can occur suddenly, and up to two-thirds of the serious pulmonary haemorrhages resulted in a fatal outcome (see section 2.4.1 Warnings and Precautions, General).Gastrointestinal haemorrhages, including rectal bleeding and melena, have been reported in colorectal patients, and have been assessed as tumour-associated haemorrhages.

Tumour-associated haemorrhages were also seen rarely in other tumour types and locations and included a case of central nervous system (CNS) bleeding in patients with CNS metastases and in patients with glioblastoma.

The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomised clinical studies. In an exploratory retrospective analysis of data from 13 completed randomised trials in patients with various tumour types, 3 patients out of 91 (3.3%) with brain metastases experienced CNS bleeding (all

Grade 4) when treated with bevacizumab, compared to 1 case (Grade 5) out of 96 patients (1%) that were not exposed to bevacizumab. In two subsequent studies in patients with treated brain metastases (which included around 800 patients), one case of Grade 2 CNS haemorrhage was reported.

Intracranial haemorrhage can occur in patients with relapsed glioblastoma. In study AVF3708g, CNS haemorrhage was reported in 2.4% (2/84) of patients in the Avastin alone arm (Grade 1), and in 3.8% (3/79) of patients treated with Avastin and irinotecan (Grades 1, 2 and 4).

Across all Avastin clinical trials, mucocutaneous haemorrhages were seen in up to 50% of patients treated with Avastin. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any change in the Avastin treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous haemorrhage (e.g. epistaxis) may be dose-dependent.

There have also been less common events of minor mucocutaneous haemorrhage in other locations, such as gingival bleeding or vaginal bleeding.

Hypertension (see section 2.4.1 General [2.4 Warnings and Precautions])

An increased incidence of hypertension (all grades) of up to 34% has been observed in patients treated with Avastin compared with up to 14% in the comparator arm. In clinical trials across all indications the overall incidence of NCI-CTC Grade 3 and 4 hypertension in patients receiving Avastin ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with Avastin compared to up to 0.2% of patients treated with the same chemotherapy alone.

Hypertension was generally adequately controlled with oral antihypertensives such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers. It rarely resulted in discontinuation of Avastin treatment or hospitalisation.

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal (see also section 2.4.1 General [2.4 Warnings and Precautions]). The risk of Avastin associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Posterior Reversible Encephalopathy Syndrome (see section 2.4.1 General [2.4 Warnings and Precautions])

Two confirmed cases (0.8%) of PRES have been reported in one clinical study. Symptoms usually resolve or improve within days, although some patients have experienced neurological sequelae.

Thromboembolism (see section 2.4.1 General [2.4 Warnings and Precautions])

- Arterial thromboembolism

An increased incidence of arterial thromboembolic events was observed in patients treated with Avastin across indications including cerebrovascular accidents, myocardial infarction, transient ischaemic attacks, and other arterial thromboembolic events.

In clinical trials, the overall incidence ranged up to 5.9% in the Avastin containing arms compared with up to 1.7% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving Avastin in combination with chemotherapy compared to 0.5% of patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischaemic attacks) were reported in up to 2.3% of Avastin treated patients versus 0.5% of patients in the control group. Myocardial infarction was reported in 1.4% of Avastin treated patients versus 0.7% of patients in the observed control group.

In one clinical trial, AVF2192g, patients with metastatic colorectal cancer who were not candidates for treatment with irinotecan were included. In this trial arterial thromboembolic events were observed in 11% (11/100) of Avastin patients compared to 5.8% (6/104) in the chemotherapy control group. In an uncontrolled clinical trial, AVF3708g in patients with relapsed glioblastoma, arterial thromboembolic events were observed in 6.3% (5/79) of patients who received Avastin in combination with irinotecan compared to 4.8% (4/84) of patients who received Avastin alone.

- **Venous thromboembolism (see section 2.4.1 General [2.4 Warnings and Precautions])**

In clinical trials across indications, the overall incidence of venous thromboembolic events ranged from 2.8% to 17.3% in the Avastin containing arms compared to 3.2% to 15.6% in the chemotherapy control arms. Venous thromboembolic events include deep venous thrombosis and pulmonary embolism.

Grade 3–5 venous thromboembolic events have been reported in up to 7.8% of patients treated with chemotherapy + bevacizumab compared with up to 4.9% in patients with chemotherapy alone. Patients who have experienced a venous thromboembolic event may be at higher risk for a recurrence if they receive Avastin in combination with chemotherapy versus chemotherapy alone.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), Grade 3–5 venous thromboembolic events have been reported in up to 10.6% of patients treated with chemotherapy and bevacizumab compared with up to 5.4% in patients with chemotherapy alone.

In clinical trial BO21990, Grade 3–5 venous thromboembolic events were observed in 7.6% of patients with newly diagnosed glioblastoma treated with Avastin in combination with chemotherapy and radiotherapy compared to 8.0% of patients treated with chemotherapy and radiotherapy alone.

Congestive Heart Failure (see section 2.4.1 General [2.4 Warnings and Precautions])

In clinical trials with Avastin, congestive heart failure (CHF) was observed in all cancer indications studied to date, but occurred predominantly in patients with metastatic breast cancer. In four phase III studies (AVF2119g, E2100, BO17708 and AVF3694g) in patients with metastatic breast cancer, CHF Grade 3 or higher was reported in up to 3.5% of patients treated with Avastin in combination with chemotherapy compared with up to 0.9% in the control arms. For patients in study AVF3694g who received anthracyclines concomitantly with bevacizumab, the incidences of Grade 3 or higher CHF for the respective bevacizumab and control arms were similar to those in the other studies on metastatic breast cancer: 2.9% in the anthracycline + bevacizumab arm and 0% in the anthracycline + placebo arm. In addition, in study AVF3694g the

incidences of all-grade CHF were similar between the anthracycline + Avastin (6.2%) and the anthracycline + placebo arms (6.0%).

Most patients who developed CHF during mBC trials showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In most clinical trials of Avastin, patients with pre-existing CHF of NYHA II – IV were excluded; therefore, no information is available on the risk of CHF in this population.

Prior anthracycline exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF (see section 2.4.1 General [2.4 Warnings and Precautions]).

An increased incidence of CHF has been observed in a clinical trial of patients with diffuse large B-cell lymphoma when receiving bevacizumab with a cumulative doxorubicin dose greater than 300 mg/m^2. This phase III clinical trial compared rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) + bevacizumab to R-CHOP without bevacizumab. While the incidence of CHF was, in both arms, above that previously observed for doxorubicin therapy, the rate was higher in the R-CHOP + bevacizumab arm.

Wound Healing (see section 2.4.1 General [2.4 Warnings and Precautions])

As Avastin may adversely impact wound healing, patients who had major surgery within the last 28 days prior to starting Avastin treatment were excluded from participation in phase III trials.

Across mCRC clinical trials there was no increased risk of post-operative bleeding or wound-healing complications observed in patients who underwent major surgery between 28 and 60 days prior to starting Avastin therapy. An increased incidence of post-operative bleeding or wound-healing complications occurring within 60 days of major surgery was observed if the patient was being treated with Avastin at the time of surgery. The incidence varied between 10% (4/40) and 20% (3/15).

Cases of serious wound-healing complications have been reported during Avastin use, some of which had a fatal outcome (see section 2.4.1 General [2.4 Warnings and Precautions]).

In locally recurrent and metastatic breast cancer trials, Grade 3-5 wound-healing complications were observed in up to 1.1% of patients receiving Avastin compared with up to 0.9% of patients in the control arms.

In the study of patients with relapsed glioblastoma (study AVF3708g), the incidence of post-operative wound-healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) was 3.6% in patients treated with single-agent Avastin and 1.3% in patients treated with Avastin plus irinotecan.

In patients with newly diagnosed glioblastoma (study BO21990) the incidence of Grade 3–5 post-operative wound-healing complications (including complications following craniotomy) was 3.3% when treated with Avastin in combination with chemotherapy and radiotherapy, compared with 1.6% when treated with chemotherapy and radiotherapy alone.

Proteinuria (see section 2.4.1 General [2.4 Warnings and Precautions])

In clinical trials, proteinuria has been reported within the range of 0.7% to 38% of patients receiving Avastin. Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome. Grade 3 proteinuria was reported in up to 8.1% of treated patients. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients.

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with Avastin. There is evidence suggesting that Grade 1 proteinuria may be related to Avastin dose. Testing for proteinuria is recommended prior to start of Avastin therapy. In most clinical studies urine protein levels of ≥ 2 g/24 h led to the holding of Avastin until recovery to <2 g/24 h.

Hypersensitivity reactions, anaphylactic reactions (including anaphylactic shock), infusion-related reactions (see section 2.4.1 Warnings and Precautions, General and section 2.6.2 Undesirable Effects, Postmarketing Experience) In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving Avastin in combination with chemotherapies than with chemotherapy alone. The incidence of these reactions in some clinical trials of Avastin is common (up to 5% in bevacizumab-treated patients).

Ovarian Failure / Fertility (see sections 2.4.1 General [2.4 Warnings and Precautions] and 2.5.1 Females and Males of Reproductive Potential [2.5 Use in Special Populations])

The incidence of new cases of ovarian failure, defined as amenorrhoea lasting 3 or more months, FSH level ≥30 mIU/ml and a negative serum β-HCG pregnancy test, has been evaluated. New cases of ovarian failure were reported more frequently in patients receiving bevacizumab. After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of women. Long-term effects of the treatment with bevacizumab on fertility are unknown.

Infections (see section 2.4.1 General [2.4 Warnings and Precautions])

In clinical trial BO21990 a randomised, double-blind, placebo-controlled, multicentre phase III study of Avastin in combination with chemotherapy plus radiotherapy for the treatment of patients with newly diagnosed glioblastoma, the incidence of all-grade and Grade 3–5 infections was 54.4% and 12.8% in the bevacizumab plus chemotherapy and radiotherapy arm versus 39.1% and 7.8% in the chemotherapy plus radiotherapy only arm, respectively.

Elderly Patients

In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events including cerebrovascular accidents, transient ischaemic attacks and myocardial infarction as compared to those aged ≤65 years when treated with Avastin (see sections 2.4.1 General [2.4 Warnings and Precautions] and 2.6.1 Clinical Trials [2.6 Undesirable Effects], Thromboembolism). Other reactions with a higher frequency seen in patients over 65 years were Grade 3–4 leucopenia and thrombocytopenia, and all-grade neutropenia, diarrhoea, nausea, headache and fatigue.

From a clinical trial in patients with metastatic colorectal cancer (study AVF2107), no increase in the incidences of other reactions, including gastrointestinal perforation, wound-healing

complications, congestive heart failure and haemorrhage was observed in elderly patients (> 65 years) receiving Avastin as compared to those aged ≤ 65 years treated with Avastin.

Laboratory Abnormalities

Decreased neutrophil count, decreased white blood cell count and presence of urine protein may be associated with Avastin treatment.

Across clinical trials, the following Grade 3 and 4 laboratory abnormalities were seen with an increased (≥2%) incidence in patients treated with Avastin compared to those in the control groups: hyperglycaemia, decreased haemoglobin, hyperkalaemia, hyponatraemia, decreased white blood cell count, increased PT (prothrombin time), normalised ratio.

Clinical trials have shown that transient increases in serum creatinine (ranging between 1.5-1.9 times baseline level), both with and without proteinuria, are associated with the use of Avastin. The observed increase in serum creatinine was not associated with a higher incidence of clinical manifestations of renal impairment in patients treated with Avastin.

2.6.2 Postmarketing Experience

The following adverse drug reactions have been identified from postmarketing experience with Avastin (Table 2) based on spontaneous case reports and literature cases. Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 2 Adverse drug reactions from postmarketing experience

Adverse reactions	Frequency Category	Reference
Infections and Infestations		
Necrotising fasciitis[1, 2]	Rare	107
Nervous system disorders		
Hypertensive encephalopathy[2,3]	Very rare	35
Posterior Reversible Encephalopathy Syndrome (PRES)[2]	Rare	36
Vascular Disorders		
Renal Thrombotic Microangiopathy, clinically manifested as proteinuria[2,3]	Unknown	71,72
Respiratory, thoracic and mediastinal disorders		
Nasal septum perforation	Unknown	49
Pulmonary hypertension	Unknown	55
Dysphonia	Common	66
Gastrointestinal disorders		
Gastrointestinal ulcer	Unknown	82
Hepatobiliary disorders		
Gallbladder perforation	Unknown	101
Musculoskeletal and Connective Tissue disorders		

Osteonecrosis of the Jaw (ONJ)[4]	Unknown	87
Osteonecrosis at sites other than the jaw[5,6]	Unknown	118
Congenital, familial and genetic disorders		
Foetal abnormalities[7]	Unknown	115

1 Usually secondary to wound healing complications, gastrointestinal perforation or fistula formation
2 See section 2.4.1 Warnings and Precautions, General
.
3 See section 2.6.1 Undesirable Effects, Clinical Trials
4 Cases of ONJ observed in Avastin-treated patients mainly in association with prior or concomitant use of bisphosphonates.
5 Cases observed in Avastin-treated pediatric patients.See section 2.5.4 Use in special populations, Pediatric use
6 Osteonecrosis observed in pediatric population in non-company clinical trials was identified through post-marketing surveillanceand has therefore been added to the post-marketing section as neither CTC grade nor reporting rate were available from published data.
7Cases have been observed in women treated with bevacizumab alone or in combinationwith known embryotoxic chemotherapeutics. See section 2.5.2 Use in Special Populations, Pregnancy.

Description of selected adverse drug reactions from postmarketing experience

Eye disorders (reported from unapproved intravitreal use)

Infectious endophthalmitis[4] (frequency not known; some cases leading to permanent blindness; one case reported extraocular extension of infection resulting in meningoencephalitis); Intraocular inflammation (some cases leading to permanent blindness; including a cluster of serious eye inflammation leading to blindness after compounding an anticancer chemotherapy product for intravenous administration) such as sterile endophthalmitis, uveitis, and vitritis; Retinal detachment (frequency not known); Retinal pigment epithelial tear (frequency not known); Intraocular pressure increased (frequency not known); Intraocular hemorrhage such as vitreous hemorrhage or retinal hemorrhage (frequency not known); Conjunctival hemorrhage (frequency not known).

An observational claims database–study comparing unapproved intravitreal Avastin to an approved treatment in patients treated for wet age-related macular degeneration has reported an increased risk of intraocular inflammation for Avastin (adjusted HR: 1.82; 99% CI: 1.20, 2.76) (Incidence 0.46 events per 100 patients per year; comparator 0.26 events per 100 patients per year) as well as an increased risk for cataract surgery (adjusted HR: 1.11; 99% CI: 1.01, 1.23) (Incidence 6.33 events per 100 patients per year; comparator 5.64 events per 100 patients per year).

Following variable and non-validated methods in compounding, storage, and handling of Avastin, serious ocular adverse events (including infectious endophthalmitis and other ocular inflammatory conditions) affecting multiple patients have been reported.

Systemic Events (reported from unapproved intravitreal use)

An observational claims database–study comparing unapproved intravitreal Avastin to an approved treatment in patients treated for wet age-related macular degeneration has reported an

increased risk of hemorrhagic stroke for Avastin (adjusted HR: 1.57; 99% CI: 1.04, 2.37) (Incidence 0.41 events per 100 patients per year; comparator 0.26 events per 100 patients per year) as well as an increased risk for overall mortality (adjusted HR: 1.11; 99% CI: 1.01, 1.23) (Incidence 6.03 events per 100 patients per year; comparator 5.51 events per 100 patients per year).

A second observational study found similar results for all-cause mortality. A randomized controlled clinical trial comparing unapproved Avastin to an approved treatment for patients with wet age-related macular degeneration3 has reported an increased risk of serious systemic adverse events for Avastin, most of which resulted in hospitalization (adjusted risk ratio 1.29; 95% CI: 1.01, 1.66) (Incidence 24.1%; comparator 19.0%).

2.7 Overdose

The highest dose tested in humans (20 mg/kg of body weight every 2 weeks, i.v.) was associated with severe migraine in several patients.

2.8 Interactions with other Medicinal Products and other Forms of Interaction

Effect of Antineoplastic Agents on Bevacizumab Pharmacokinetics

No clinically relevant pharmacokinetic (PK) interactions of co-administered chemotherapy on Avastin pharmacokinetics has been observed based on the results of a population PK analysis. There was neither statistical significance nor clinically relevant difference in clearance of Avastin in patients receiving Avastin monotherapy compared to patients receiving Avastin in combination with interferon alfa-2a or other chemotherapies (irinotecan/bolus 5-fluorouracil/leucovorin [IFL], 5-fluorouracil/leucovorin [5-FU/LV], carboplatin/paclitaxel, capecitabine, doxorubicin or cisplatin/gemcitabine).

Effect of Bevacizumab on the Pharmacokinetics of other Antineoplastic Agents

No clinically relevant interaction of bevacizumab was observed on the pharmacokinetics of co-administered interferon‒alfa 2a, erlotinib (and its active metabolite OSI-420), or the chemotherapies irinotecan (and its active metabolite SN38), capecitabine, oxaliplatin (as determined by measurement of free and total platinum), and cisplatin. Conclusions on the impact of bevacizumab on gemcitabine pharmacokinetics cannot be drawn.

Combination of Bevacizumab and Sunitinib Malate

In two clinical studies of metastatic renal cell carcinoma, microangiopathic haemolytic anaemia (MAHA) was reported in 7 out of 19 patients treated with bevacizumab (10 mg/kg every 2 weeks) and sunitinib malate (50 mg daily) combination.

MAHA is a haemolytic disorder which can present with red cell fragmentation, anaemia and thrombocytopenia. In addition, hypertension (including hypertensive crisis), elevated creatinine and neurological symptoms were observed in some of these patients. All of these findings were reversible upon discontinuation of bevacizumab and sunitinib malate (see section 2.4.1 General [2.4 Warnings and Precautions], Hypertension, PRES, Proteinuria).

Radiotherapy

The safety and efficacy of concomitant administration of chemotherapy (temozolomide), radiotherapy and Avastin was evaluated in study BO21990, a phase III, randomised, double-blind, placebo-controlled study of 921 patients with newly diagnosed glioblastoma. No new adverse events associated with Avastin were reported in this study.

The safety and efficacy of concomitant administration of radiotherapy and Avastin has not been established in other indications.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Avastin (bevacizumab) is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biological activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with antigen-binding regions of a humanised murine antibody that binds to VEGF. Bevacizumab is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system, and is purified by a process that includes specific viral inactivation and removal steps. Bevacizumab consists of 214 amino acids and has a molecular weight of approximately 149,000 daltons.

Avastin inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralising the biological activity of VEGF reduces the vascularisation of tumours, thereby inhibiting tumour growth. Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive antitumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

3.1.2 Clinical / Efficacy Studies

Metastatic Colorectal Cancer (mCRC)

The safety and efficacy of the recommended dose of Avastin (5 mg/kg of body weight every 2 weeks) in metastatic carcinoma of the colon or rectum were studied in three randomised, active-controlled clinical trials in combination with fluoropyrimidine-based first-line chemotherapy. Avastin was combined with two chemotherapy regimens:

- **AVF2107g:** A weekly schedule of irinotecan/bolus 5-fluorouracil/leucovorin (IFL regimen) for a total of 4 weeks of each 6-week cycle.
- **AVF0780g:** In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV) for a total of 6 weeks of each 8-week cycle (Roswell Park regimen).
- **AVF2192g:** In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV) for a total of 6 weeks of each 8-week cycle (Roswell Park regimen) in patients who were not optimal candidates for first-line irinotecan treatment.

Three additional studies with Avastin have been conducted in mCRC patients: first-line (NO16966), second-line with no previous Avastin treatment (E3200), and second-line with previous Avastin treatment following disease progression in first-line (ML18147). In these

studies, Avastin was administered at the following dosing regimens, in combination with FOLFOX-4 (5-FU/LV/oxaliplatin), XELOX (capecitabine/oxaliplatin), and fluoroprymidine/irinotecan and fluoroprymidine/oxaliplatin:

- **NO16966:** Avastin 7.5 mg/kg of body weight every 3 weeks in combination with oral capecitabine and i.v. oxaliplatin (XELOX) or Avastin 5 mg/kg every 2 weeks in combination with leucovorin + 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with i.v. oxaliplatin (FOLFOX-4).
- **E3200:** Avastin 10 mg/kg of body weight every 2 weeks in combination with leucovorin and 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with i.v. oxaliplatin (FOLFOX-4) in Avastin naïve patients.
- **ML18147:** Avastin 5.0 mg/kg of body weight every 2 weeks or Avastin 7.5 mg/kg of body weight every 3 weeks in combination with fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin in patients with disease progression following first-line treatment with Avastin. Use of irinotecan- or oxaliplatin-containing regimen was switched depending on first-line usage of either oxaliplatin or irinotecan.

AVF2107g

This was a phase III randomised, double-blind, active-controlled clinical trial evaluating Avastin in combination with IFL as first-line treatment for metastatic carcinoma of the colon or rectum. Eight hundred and thirteen patients were randomised to receive IFL + placebo (Arm 1) or IFL + Avastin (5 mg/kg every 2 weeks, Arm 2). A third group of 110 patients received bolus 5-FU/LV + Avastin (Arm 3). Enrolment in Arm 3 was discontinued, as prespecified, once safety of Avastin with the IFL regimen was established and considered acceptable.

The primary efficacy parameter of the trial was overall survival. The addition of Avastin to IFL resulted in statistically significant increases in overall survival, progression-free survival and overall response rate (see Table 3 for details). The clinical benefit of Avastin, as measured by survival, was seen in all pre-specified patient subgroups, including those defined by age, sex, performance status, location of primary tumour, number of organs involved, and duration of metastatic disease.

Table 3 Efficacy Results from Study AVF2107g

	AVF2107g	
	Arm 1 IFL □ placebo	**Arm 2 IFL □ Avastin[a]**
Number of patients	411	402
Overall survival		
Median (months)	15.6	20.3
95% confidence interval	14.29 – 16.99	18.46 – 24.18
Hazard ratio[b]	0.660 (p-value = 0.00004)	
Secondary endpoint: progression-free survival		
Median (months)	6.2	10.6
Hazard ratio	0.54 (p-value □ 0.00001)	
Overall response rate	34.8%	44.8%
	(p-value = 0.0036)	

[a] 5 mg/kg every 2 weeks
[b] Relative to control arm

Among the 110 patients randomised to arm 3 (5-FU/LV + Avastin) prior to discontinuation of this arm, the median overall survival was 18.3 months and the median progression-free survival was 8.8 months.

AVF2192g

This was a phase II randomised, double-blind, active-controlled clinical trial investigating Avastin in combination with 5-FU/leucovorin as first-line treatment for metastatic colorectal cancer in patients who were not optimal candidates for first-line irinotecan treatment. One hundred and five patients were randomised to 5-FU/LV + placebo arm and 104 patients randomised to 5-FU/LV + Avastin (5 mg/kg every 2 weeks). All treatments were continued until disease progression.

The addition of Avastin 5 mg/kg every 2 weeks to 5-FU/LV resulted in higher objective response rates, significantly longer progression-free survival, and a trend in longer survival, as compared with 5-FU/LV chemotherapy alone.

NO16966

This was a phase III randomised, double-blind (for bevacizumab) clinical trial investigating Avastin 7.5 mg/kg in combination with oral capecitabine and i.v. oxaliplatin (XELOX), administered on a 3-weekly schedule; or Avastin 5 mg/kg in combination with leucovorin with 5-fluorouracil bolus, followed by 5-fluorouracil infusional, with i.v. oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule. The study contained two parts: an initial unblinded 2-arm part (Part I) in which patients were randomised to two different treatment groups (XELOX and FOLFOX-4) and a subsequent 2 x 2 factorial 4-arm part (Part II) in which patients were randomised to four treatment groups (XELOX + placebo, FOLFOX-4 + placebo, XELOX + Avastin, FOLFOX-4 + Avastin). In Part II, treatment assignment was double-blind with respect to Avastin.

Approximately 350 patients were randomised to each of the four study arms in the Part II of the trial.

Table 4 Treatment Regimens in Study NO16966 (mCRC)

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + Avastin	Oxaliplatin	85 mg/m^2 i.v. 2 h	Oxaliplatin on Day 1
	Leucovorin	200 mg/m^2 i.v. 2 h	Leucovorin on Days 1 and 2
	5-fluorouracil	400 mg/m^2 i.v. bolus, 600 mg/m^2 i.v. 22 h	5-fluorouracil i.v. bolus/infusion, each on Days 1 and 2
	Placebo or Avastin	5 mg/kg i.v. 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX + Avastin	Oxaliplatin	130 mg/m^2 i.v. 2 h	Oxaliplatin on Day 1
	Capecitabine	1000 mg/m^2 oral bid	Capecitabine oral bid for 2 weeks (followed by 1 week off treatment)
	Placebo or Avastin	7.5 mg/kg i.v. 30-90 min	Day 1, prior to XELOX, q 3 weeks

5-fluorouracil: i.v. bolus injection immediately after leucovorin

The primary efficacy parameter of the trial was the duration of progression-free survival. In this study, there were two primary objectives: to show that XELOX was non-inferior to FOLFOX-4 and to show that Avastin in combination with FOLFOX-4 or XELOX chemotherapy was superior to chemotherapy alone. Both co-primary objectives were met:

i) Non-inferiority of the XELOX-containing arms compared with the FOLFOX-4-containing arms in the overall comparison was demonstrated in terms of progression-free survival and overall survival in the eligible per-protocol population.

ii) Superiority of the Avastin containing arms versus the chemotherapy alone arms in the overall comparison was demonstrated in terms of progression-free survival in the intent-to-treat (ITT) population (Table 5).

Secondary progression-free survival (PFS) analyses, based on Independent Review Committee (IRC)- and "on-treatment"-based response assessments, confirmed the significantly superior clinical benefit for patients treated with Avastin (subgroup analyses shown in Table 5), consistent with the statistically significant benefit observed in the pooled analysis.

Table 5 Key Efficacy Results from the Superiority Analysis (ITT Population, Study NO16966)

Endpoint (months)	**FOLFOX-4 or XELOX + placebo (n=701)**	**FOLFOX-4 or XELOX + bevacizumab (n=699)**	**p-Value**
Primary endpoint			
Median PFS**	8.0	9.4	0.0023
Hazard ratio (97.5% CI)[a]	0.83 (0.72–0.95)		
Secondary endpoints			
Median PFS (on treatment)**	7.9	10.4	<0.0001
Hazard ratio (97.5% CI)	0.63 (0.52–0.75)		
Median PFS (indep. review)**	8.5	11.0	<0.0001
Hazard ratio (97.5% CI)	0.70 (0.58–0.83)		
Overall response rate (invest. assessment)**	49.2%	46.5%	
Overall response rate (indep. review)**	37.5%	37.5%	
Median overall survival*	19.9	21.2	0.0769
Hazard ratio (97.5% CI)	0.89 (0.76–1.03)		

* Overall survival analysis at clinical cut-off 31 January 2007
** Primary analysis at clinical cut-off 31 January 2006
[a] Relative to control arm

ECOG E3200

This was a phase III randomised, active-controlled, open-label study investigating Avastin 10 mg/kg in combination with leucovorin with 5-fluorouracil bolus and then 5-fluorouracil infusional, with i.v. oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule in previously treated patients (second-line) with advanced colorectal cancer. In the chemotherapy arms, the FOLFOX-4 regimen used the same doses and schedule as shown in Table 4 for study NO16966.

The primary efficacy parameter of the trial was overall survival, defined as the time from randomisation to death from any cause. Eight hundred and twenty-nine patients were randomised (292 FOLFOX-4, 293 Avastin + FOLFOX-4 and 244 Avastin monotherapy). The addition of Avastin to FOLFOX-4 resulted in a statistically significant prolongation of survival. Statistically

significant improvements in progression-free survival and objective response rate were also observed (see Table 6).

Table 6 Efficacy Results from Study E3200

	E3200	
	FOLFOX-4	**FOLFOX-4 Avastin**[a]
Number of patients	292	293
Overall survival		
Median (months)	10.8	13.0
95% confidence interval	10.12 – 11.86	12.09 – 14.03
Hazard ratio[b]	0.751 (p-value = 0.0012)	
Progression-free survival		
Median (months)	4.5	7.5
Hazard ratio	0.518 (p-value 0.0001)	
Objective response rate		
Rate	8.6%	22.2%
	(p-value)	

[a] 10 mg/kg every 2 weeks
[b] Relative to control arm

No significant difference was observed in the duration of overall survival between patients who received Avastin monotherapy compared to patients treated with FOLFOX-4. Progression-free survival and objective response rate were inferior in the Avastin monotherapy arm compared to the FOLFOX-4 arm.

ML18147

This was a phase III randomised, controlled, open-label trial investigating Avastin 5.0 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks in combination with fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone in patients with metastatic colorectal cancer who progressed on a first-line Avastin-containing regimen. Patients with histologically confirmed mCRC and disease progression were randomised 1:1 within 3 months after discontinuation of Avastin first-line therapy to receive fluoropyrimidine/oxaliplatin or fluoropyrimidine/irinotecan-based chemotherapy (chemotherapy switched depending on first-line chemotherapy) with or without Avastin. Treatment was given until progressive disease or unacceptable toxicity. The primary outcome measure was overall survival (OS) defined as the time from randomisation until death from any cause.

A total of 820 patients were randomised. The addition of Avastin to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of survival in patients with metastatic colorectal cancer who progressed on a first-line Avastin-containing regimen (ITT = 819) (see Table 7).

Table 7Efficacy Results for Study ML18147

	ML18147	
	Fluoropyrimidine/irinotecan or fluoropyrimidine/oxaplatin-based chemotherapy	**Fluoropyrimidine/irinotecan or fluoropyrimidine/oxaplatin-based chemotherapy + Avastin[a]**
Number of patients	410	409
Overall Survival		
Median (months)	9.8	11.2
95% confidence interval	9-11	10-12
Hazard ratio	0.81 (p-value = 0.0062)	
Progression-Free Survival		
Median (months)	4.1	5.7
Hazard ratio	0.68 (p-value < 0.0001)	
Objective Response Rate (ORR)		
Rate	3.9%	5.4%
	(p-value = 0.3113)	

[a] 2.5 mg/kg/week

Statistically significant improvements in progression-free survival were also observed. Objective response rate was low in both treatment arms and did not meet statistical significance.

Adjuvant Chemotherapy for Colon Cancer (aCC)

BO17920

This was a phase III randomised open-label, 3-arm study evaluating the efficacy and safety of Avastin administered at a dose equivalent to 2.5 mg/kg/week on either a 2-weekly schedule in combination with FOLFOX-4, or on a 3-weekly schedule in combination with XELOX versus FOLFOX-4 alone as adjuvant chemotherapy in 3451 patients with high-risk stage II and stage III colon carcinoma.

More relapses and deaths due to disease progression were observed in both Avastin arms compared to the control arm. The primary objective of prolonging disease-free survival (DFS) in patients with stage III colon cancer (n = 2867) by adding Avastin to either chemotherapy regimen was not met. The hazard ratios for DFS were 1.17 (95% CI: 0.98-1.39) for the FOLFOX-4 + Avastin arm and 1.07 (95% CI: 0.90-1.28) for the XELOX + Avastin arm.

Locally Recurrent or Metastatic Breast Cancer (mBC)

ECOG E2100

E2100 was an open-label, randomised, active-controlled, multicenter clinical trial evaluating Avastin in combination with paclitaxel for locally recurrent or metastatic breast cancer in patients who had not previously received chemotherapy for locally recurrent and metastatic disease. Prior hormonal therapy for the treatment of metastatic disease was allowed. Adjuvant taxane therapy was allowed only if it was completed at least 12 months prior to study entry.

Patients were randomised to paclitaxel alone (90 mg/m^2 i.v. over 1 hour once weekly for 3 out of 4 weeks) or in combination with Avastin (10 mg/kg i.v. infusion every 2 weeks). Patients were to continue assigned study treatment until disease progression. In cases where patients discontinued chemotherapy prematurely, treatment with Avastin as a single agent was continued until disease progression. The primary endpoint was progression-free survival (PFS), as assessed by investigators. In addition, an independent review of the primary endpoint was also conducted.

Of the 722 patients in the study, the majority of patients (90%) had HER2-negative disease. A small number of patients had HER2 receptor status that was either unknown (8%) or positive (2%). Patients who were HER2-positive had either received previous treatment with trastuzumab or were considered unsuitable for trastuzumab. The majority (65%) of patients had received adjuvant chemotherapy including 19% who had prior taxanes and 49% who had prior anthracyclines. The patient characteristics were similar between the study arms.

The results of this study are presented in Table 8.

Table 8 Study E2100 Efficacy Results: Eligible Patients

Progression-free survival				
	Investigator assessment*		**IRF assessment**	
	Paclitaxel (n=354)	**Paclitaxel/Avastin (n=368)**	**Paclitaxel (n=354)**	**Paclitaxel/Avastin (n=368)**
Median PFS (months)	5.8	11.4	5.8	11.3
HR (95% CI)	0.421 (0.343; 0.516)		0.483 (0.385; 0.607)	
p-Value	<0.0001		<0.0001	
Response rates (for patients with measurable disease)				
	Investigator assessment		**IRF assessment**	
	Paclitaxel (n=273)	**Paclitaxel/Avastin (n=252)**	**Paclitaxel (n=243)**	**Paclitaxel/Avastin (n=229)**
% pts with objective response	23.4	48.0	22.2	49.8
p-Value	<0.0001		<0.0001	
Overall survival				
	Paclitaxel (n=354)		**Paclitaxel/Avastin (n=368)**	
Median OS (months)	24.8		26.5	

HR (95% CI)	0.869 (0.722; 1.046)
p-Value	0.1374

* Primary analysis

BO17708

BO17708 was a randomised, double-blind, placebo-controlled, multicenter (phase III) trial to evaluate the efficacy and safety of Avastin in combination with docetaxel compared with docetaxel + placebo as first-line treatment for patients with HER2-negative metastatic or locally recurrent breast cancer who have not received prior chemotherapy for their metastatic disease.

Patients were randomised in a 1:1:1 ratio to treatment with either one of the following:

- Placebo + docetaxel 100 mg/m^2 every 3 weeks
- Avastin 7.5 mg/kg + docetaxel 100 mg/m^2 every 3 weeks
- Avastin 15 mg/kg + docetaxel 100 mg/m^2 every 3 weeks.

Docetaxel treatment was limited to a maximum of 9 cycles, while Avastin or placebo was continued until disease progression/death or unacceptable toxicity. The patient and disease characteristics were similar across the three arms.

On documented disease progression, patients from all three treatment arms could enter into a post-study treatment phase during which they received open-label Avastin together with a wide range of second-line therapies.

The primary endpoint was progression-free survival (PFS), as assessed by investigators. For the efficacy endpoints two comparisons were performed:

- Avastin 7.5 mg/kg + docetaxel 100 mg/m^2 every 3 weeks versus placebo + docetaxel 100 mg/m^2 every 3 weeks
- Avastin 15 mg/kg + docetaxel 100 mg/m^2 every 3 weeks versus placebo + docetaxel 100 mg/m^2 every 3 weeks.

The results of this study are presented in Table 9. For progression-free survival and response rates this included results from the prespecified final analysis and results from an exploratory (updated) analysis carried out at the same time as the prespecified final OS analysis which included an additional 18 months of follow-up. Overall survival results presented are those from the prespecified final analysis for OS. At this point approximately 45% of patients across all treatment arms had died.

The updated analysis shows:

- Avastin 15 mg/kg q 3 weeks + docetaxel is consistently associated with better primary and secondary efficacy outcomes with similar safety compared with Avastin 7.5 mg/kg q 3 weeks + docetaxel
- Avastin 7.5 mg/kg q 3 weeks + docetaxel is not superior to control for PFS and response rates.

Therefore the 15 mg/kg q 3 weeks dose is recommended for treatment in patients with mBC (see section 2.2 Dosage and Administration).

Table 9Efficacy Results from Study BO17708

Progression-free survival			
	Docetaxel + placebo q 3 weeks (n=241)	**Docetaxel + Avastin 7.5 mg/kg q 3 weeks (n=248)**	**Docetaxel + Avastin 15 mg/kg q 3 weeks (n=247)**
Median PFS (months) [updated analysis]	8.0 [8.2]	8.7 [9.0]	8.8 [10.1]
Hazard ratio vs placebo arm (95% CI) [updated analysis]		0.79 (0.63–0.98) [0.86] [0.72; 1.04]	0.72 (0.57–0.90) [0.77] [0.64; 0.93]
p-Value (log-rank test) vs placebo arm [exploratory p-value from updated analysis]		0.0318 [0.1163]	0.0099 [0.0061]
Progression-free survival (sensitivity analysis)*			
	Docetaxel + placebo q 3 weeks (n=241)	**Docetaxel + Avastin 7.5 mg/kg q 3 weeks (n=248)**	**Docetaxel + Avastin 15 mg/kg q 3 weeks (n=247)**
Median PFS (months) [updated analysis]	8.0 [8.1]	8.7 [9.0]	8.8 [10.0]
Hazard ratio vs placebo arm (95% CI) [updated analysis]		0.69 (0.54–0.89) [0.80] [0.65; 1.00]	0.61 (0.48–0.78) [0.67] [0.54; 0.83]
p-Value (log-rank test) vs placebo arm [exploratory p-value from updated analysis]		0.0035 [0.0450]	0.0001 [0.0002]
Response rates (for patients with measurable disease)			
	Docetaxel + placebo q 3 weeks (n=207)	**Docetaxel + Avastin 7.5 mg/kg q 3 weeks (n=201)**	**Docetaxel + Avastin 15 mg/kg q 3 weeks (n=206)**
% pts with objective response [updated analysis]	44.4 [46.4]	55.2 [55.2]	63.1 [64.1]
p-Value vs placebo arm [exploratory p-value from		0.0295 [0.0739]	0.0001 [0.0003]

updated analysis]			
Overall survival			
	Docetaxel + placebo q 3 weeks (n=241)	**Docetaxel + Avastin 7.5 mg/kg q 3 weeks (n=248)**	**Docetaxel + Avastin 15 mg/kg q 3 weeks (n=247)**
Median OS (months)	31.9	30.8	30.2
HR (95% CI) p-Value		1.05 (0.81; 1.36) 0.7198	1.03 (0.79; 1.33) 0.8528

* Stratified analysis which included all progression and death events except those where non-protocol therapy (NPT) was initiated prior to documented progression – those patients were censored at the last tumour assessment prior to the start of NPT.

AVF3694g

Study AVF3694g was a Phase III, multicenter, randomised, placebo-controlled trial designed to evaluate the efficacy and safety of Avastin in combination with chemotherapy compared to chemotherapy plus placebo as first-line treatment for patients with HER2-negative metastatic or locally recurrent breast cancer.

Chemotherapy was chosen at the investigator's discretion prior to randomization in a 2:1 ratio to receive either chemotherapy + Avastin or chemotherapy + placebo. The choices of chemotherapy included taxane (protein-bound paclitaxel, docetaxel), anthracycline-based agents (doxorubicin/ cyclophosphamide, epirubicin/ cyclophosphamide, 5-fluorouracil/ doxorubicin/ cyclophosphamide, 5-fluorouracil/ epirubicin/ cyclophosphamide) or capecitabine given every three weeks (q3w). Avastin or placebo was administered at a dose of 15 mg/kg q3w.

This study included a blinded treatment phase, an optional open-label post-progression phase, and a survival follow-up phase. During the blinded treatment phase, patients received chemotherapy and study drug (Avastin or placebo) every 3 weeks until disease progression, treatment-limiting toxicity, or death.

On documented disease progression, patients who entered the optional open label phase could receive open label Avastin together with a wide-range of second line therapies. The percentage of patients in each arm who received open-label Avastin were: Taxane/Anth + Placebo: 43.0 %, Taxane/Anth + Avastin: 29.6% and Cap + Placebo: 51.9%, Cap + Avastin 34.7%.

Patients were analyzed in the two cohorts depending on the treatment they received as follows:

- Patients receiving taxane/anthracycline + Avastin/placebo (Taxane/Anth + Avastin/Pl) – Cohort 1
- Patients receiving capecitabine + Avastin/placebo (Cap + Avastin/Pl) – Cohort 2

The primary endpoint was progression free survival (PFS) based on investigator assessment for 1) patients receiving either taxane therapy or anthracycline-based therapy (Cohort 1); and

2) patients receiving capecitabine therapy (Cohort 2). Each cohort was independently powered. In addition, an independent review of the primary endpoint was also conducted.

The results of this study from the final protocol defined analyses for progression free survival and response rates are presented in Table 10 (Cohort 1) and Table 11 (Cohort 2). Results from an exploratory overall survival analysis which include an additional 7 months of follow-up are also presented for both cohorts. At this point approximately 45% of patients across all treatment arms had died.

Table 10 Efficacy results for study AVF3694g: Cohort 1 –Taxane/ Anthracycline and Avastin/Placebo (Taxane/Anth + Avastin/Pl)

Progression-free survival*				
	Investigator Assessment		IRC Assessment	
	Taxane/Anth + Pl (n= 207)	Taxane/Anth + Avastin (n=415)	Taxane/Anth + Pl (n= 207)	Taxane/Anth + Avastin (n=415)
Median PFS (months)	8.0	9.2	8.3	10.7
Hazard ratio vs placebo arm (95% CI)	0.64 (0.52; 0.80)		0.77 (0.60; 0.99)	
p-value	<0.0001		0.040	
Response rate (for patients with measurable disease)*				
	Taxane/Anth + Pl (n= 177)		Taxane/Anth + Avastin (n=345)	
% pts with objective response	37.9		51.3	
p-value	0.0054			
Overall survival*				
Median OS (months)	NR**		27.5	
HR (95% CI)	1.11 (0.86, 1.43)			
p-value (exploratory)	0.44			

*Stratified analysis included all progression and death events except those where non-protocol therapy (NPT) was initiated prior to documented progression; data from those patients were censored at the last tumor assessment prior to starting NPT.
** Not reached

Table 11 Efficacy results for study AVF3694g: Cohort 2 – Capecitabine and Avastin/Placebo (Cap+ Avastin/Pl)

Progression-free survival*				
	Investigator Assessment		IRC Assessment	
	Cap + Pl (n= 206)	Cap + Avastin (n=409)	Cap + Pl (n= 206)	Cap + Avastin (n=409)
Median PFS (months)	5.7	8.6	6.2	9.8
Hazard ratio vs placebo arm (95% CI)	0.69 (0.56; 0.84)		0.68 (0.54; 0.86)	

p-value	0.0002	0.0011
Response rate (for patients with measurable disease)*		
	Cap + Pl (n= 161)	Cap + Avastin (n=325)
% pts with objective response	23.6	35.4
p-value	0.0097	
Overall survival*		
Median OS (months)	22.8	25.7
HR (95% CI)	0.88 (0.69, 1.13)	
p-value (exploratory)	0.33	

*Stratified analysis included all progression and death events except those where non-protocol therapy (NPT) was initiated prior to documented progression; data from those patients were censored at the last tumor assessment prior to starting NPT.

For both cohorts, an unstratified analysis of PFS (investigator assessed) was performed that did not censor for non-protocol therapy prior to disease progression. The results of these analyses were very similar to the primary PFS results.

AVF3693g

Study AVF3693g was a Phase III, multicentre, randomised, placebo-controlled double-blinded trial designed to evaluate the efficacy and safety of Avastin in combination with chemotherapy compared with chemotherapy plus placebo for treatment of patients with metastatic breast cancer who have failed first-line chemotherapy. The choices of chemotherapy included taxane (paclitaxel, protein-bound paclitaxel, docetaxel), gemcitabine, capecitabine or vinorelbine. Chemotherapy was chosen at the investigator's discretion prior to randomisation 2:1 to receive either chemotherapy + Avastin or chemotherapy + placebo. The dose of Avastin/placebo administered in this study was 15 mg/kg intravenously every 3 weeks (q3w) or 10 mg/kg every 2 weeks (q2w), depending on the schedule of chemotherapy chosen:

- Taxane
  - Paclitaxel: 90 mg/m^2 IV every week for 3 weeks followed by 1 week of rest
  - Paclitaxel: 175 mg/m^2 IV every 3 weeks
  - Paclitaxel protein-bound particles: 260 mg/m^2 IV every 3 weeks
  - Docetaxel: 75–100 mg/m^2 IV every 3 weeks
- Gemcitabine: 1250 mg/m^2 IV on Days 1 and 8 of each 3-week cycle
- Capecitabine: 1000 mg/m^2 orally twice daily on Days 1–14 of each 3-week cycle
- Vinorelbine: 30 mg/m^2 IV every week

The study included a blinded treatment phase, an optional open-label extended treatment phase, and a survival follow-up phase. During the blinded treatment phase, patients received chemotherapy and study drug (Avastin or placebo) until disease progression, treatment-limiting toxicity, discontinuation per investigator decision, or death due to any cause.

The primary endpoint was PFS, as assessed by investigators, pooled across all chemotherapy cohorts. The results of the key endpoints in this study are summarized in Table 12. An

unstratified analysis of PFS was performed; results of this analysis was similar to those of the primary PFS analysis.

The results based on the interim analysis (57% of events) of overall survival is summarized in Table 12. This interim analysis was performed at the same time as the primary analysis of PFS.

Table 12 Efficacy results for study AVF3693g:

Progression-free survival*		
	Chemo + Placebo (n = 225)	Chemo + Avastin (n = 459)
Median PFS (months)	5.1	7.2
Hazard ratio relative to placebo (95% CI)	0.78 (0.64, 0.93)	
p-value	0.0072	
Response rate (for patients with measurable disease)*		
	Chemo + Placebo (n = 179)	Chemo + Avastin (n = 362)
% pts with objective response	29.6	39.5
p-value	0.0193**	
Interim Overall survival*		
Median OS (months)	16.4	18.0
Hazard ratio (95% CI)	0.90 (0.71, 1.14)	
p-value	0.3741	

* Stratified analysis
** Based on alpha = 0.01

The study was not powered for individual chemotherapy cohorts however progression-free-survival by chemotherapy cohorts was a pre-specified secondary endpoint. All the chemotherapy cohorts were consistent with the primary results except for the smallest chemotherapy cohort of vinorelbine (n=76).

Advanced, Metastatic or Recurrent Non-Small Cell Lung Cancer (NSCLC)

The safety and efficacy of Avastin in the first-line treatment of patients with non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology was studied in addition to platinum-based chemotherapy in studies E4599 and BO17704.

E4599

E4599 was an open-label, randomised, active-controlled, multicentre clinical trial evaluating Avastin as first-line treatment of patients with locally advanced, metastatic or recurrent NSCLC other than predominantly squamous cell histology.

Patients were randomised to platinum-based chemotherapy (paclitaxel 200 mg/m^2 and carboplatin AUC = 6.0, both by i.v. infusion) (PC) on Day 1 of every 3-week cycle for up to 6 cycles or PC in combination with Avastin at a dose of 15 mg/kg i.v. infusion on Day 1 of every 3-week cycle. After completion of 6 cycles of carboplatin-paclitaxel chemotherapy or upon premature discontinuation of chemotherapy, patients on the Avastin + carboplatin-paclitaxel arm continued to receive Avastin as a single agent every 3 weeks until disease progression. Eight hundred and seventy-eight patients were randomised to the two arms.

During the study, of the patients who received trial treatment, 32.2% (136/422) of patients received 7–12 administrations of Avastin and 21.1% (89/422) of patients received 13 or more administrations of Avastin.

The primary endpoint was duration of survival. Results are presented in Table 13.

Table 13 Efficacy Results from Study E4599

	Arm 1 **Carboplatin/ paclitaxel**	**Arm 2** **Carboplatin/ paclitaxel + Avastin 15 mg/kg q 3 weeks**
Number of patients	444	434
Overall survival		
Median (months)	10.3	12.3
Hazard ratio		0.80 (p=0.003) 95% CI (0.69, 0.93)
Progression-free survival		
Median (months)	4.8	6.4
Hazard ratio		0.65 (p<0.0001) 95% CI (0.56, 0.76)
Overall response rate		
Rate (percent)	12.9	29.0 (p<0.0001)

BO17704

Study BO17704 was a randomised, double-blind phase III study of Avastin in addition to cisplatin and gemcitabine versus placebo, cisplatin and gemcitabine in patients with locally advanced, metastatic or recurrent non-squamous NSCLC who had not received prior chemotherapy. The primary endpoint was progression-free survival; secondary endpoints for the study included the duration of overall survival.

Patients were randomised to platinum-based chemotherapy, cisplatin 80 mg/m^2 i.v. infusion on day 1 and gemcitabine 1250 mg/m^2 i.v. infusion on days 1 and 8 of every 3-week cycle for up to 6 cycles (CG) with placebo or CG with Avastin at a dose of 7.5 or 15 mg/kg i.v. infusion on day 1 of every 3-week cycle. In the Avastin containing arms, patients could receive Avastin as a single agent every 3 weeks until disease progression or unacceptable toxicity.

Study results show that 94% (277/296) of eligible patients went on to receive single-agent bevacizumab at cycle 7. A high proportion of patients (approximately 62%) went on to receive a variety of non-protocol specified anticancer therapies, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 14.

Table 14 Efficacy Results from Study BO17704

	Cisplatin/gemcitabine + placebo	**Cisplatin/gemcitabine + Avastin 7.5 mg/kg q 3 weeks**	**Cisplatin/gemcitabine + Avastin 15 mg/kg q 3 weeks**
Number of patients	347	345	351
Progression-free survival			
Median (months)	6.1	6.7 (p = 0.0026)	6.5 (p = 0.0301)
Hazard ratio		0.75 [0.62; 0.91]	0.82 [0.68; 0.98]
Best overall response rate [a]	20.1%	34.1% (p < 0.0001)	30.4% (p = 0.0023)
Overall survival			
Median (months)	13.1	13.6 (p = 0.4203)	13.4 (p = 0.7613)
Hazard ratio		0.93 [0.78; 1.11]	1.03 [0.86; 1.23]

[a] Patients with measurable disease at baseline

JO25567

Study JO25567 was a randomized, open-label, multi-center Phase II study conducted in Japan to evaluate the efficacy and safety of bevacizumab used in addition to erlotinib in patients with non-squamous NSCLC with EGFR activating mutations who had not received prior systemic therapy for Stage IIIB/IV or recurrent disease.

The primary endpoint was progression-free survival (PFS) based on independent review assessment. Secondary endpoints included overall survival, response rate, disease control rate,

duration of response, safety and Health Related Quality of Life based on the FACT-L (Functional Assessment of Cancer Therapy for Patients with Lung Cancer) questionnaire.

EGFR mutation status was determined for each patient prior to patient screening and 154 patients were randomised to receive either erlotinib + bevacizumab [erlotinib 150 mg oral daily + bevacizumab (15 mg/kg IV every 3 weeks)] or erlotinib monotherapy (150 mg oral daily until disease progression (PD) or unacceptable toxicity. In the absence of PD, discontinuation of one component of study treatment in the erlotinib + bevacizumab arm did not lead to discontinuation of the other component of study treatment as specified in the study protocol.

The efficacy results of the study are presented in Table 15.

Table 15 Efficacy results for study JO25567

	Erlotinib N = 77#	**Erlotinib + Bevacizumab N = 75#**
PFS^ (months)		
Median	9.7	16.0
HR (95% CI)	0.54 (0.36; 0.79)	
p-value	0.0015	
Overall Response Rate		
Rate	63.6%	69.3%
p-value	0.4951	
Duration of Response (months)		
Median	9.3	13.3
HR (95% CI)	0.68 (0.43; 1.10)	
p-value	0.118	
Disease Control Rate		
Rate	88.3%	98.7%
p-value	0.0177	
Overall Survival* (months)		
Median	NR	NR
HR (95% CI)	1.04 (0.61- 1.77)	
p-value	0.8926	

A total of 154 patients were randomized. However, two of the randomized patients discontinued the study before receiving any study treatment

^ blinded independent review (protocol-defined primary analysis)

* Exploratory analysis; OS updated analysis at clinical cut-off on Nov 2014, approx. 35% patient had died and OS is therefore considered immature.

CI, confidence interval; HR, Hazard ratio from unstratified Cox regression analysis; NR, not reached:

In the open label study JO25567, Health Related Quality of life (HRQoL) was assessed by the FACT-L total and trial outcome index (TOI) scores and lung cancer symptoms, as assessed by the FACT-L lung cancer symptom subscale (LCS). During the progression-free time, mean baseline FACT-L scores were maintained in both treatment arms. There were no clinically meaningful differences in the FACT-L HRQoL observed between the two treatment arms. Of note, patients in the erlotinib + bevacizumab arm were treated for a longer duration and received intravenous administration of bevacizumab as opposed to oral erlotinib monotherapy in the control arm.

Advanced and/or Metastatic Renal Cell Cancer (mRCC)

BO17705

Study BO17705 was a multicentre, randomised, double-blind phase III trial conducted to evaluate the efficacy and safety of Avastin in combination with interferon (IFN) alfa-2a (Roferon®) versus IFN alfa-2a alone as first-line treatment in mRCC. The 649 randomised patients (641 treated) had clear-cell mRCC, Karnofsky performance status (KPS) of ≥70%, no CNS metastases and adequate organ function. IFN alfa-2a (x3/week at a recommended dose of 9 MIU) + Avastin (10 mg/kg q2w) or placebo was given until disease progression. Patients were stratified according to country and Motzer score and the treatment arms were shown to be well balanced for the prognostic factors.

The primary endpoint was overall survival, with secondary endpoints for the study including progression-free survival. The addition of Avastin to IFN alfa-2a significantly increased PFS and objective tumour response rate. These results have been confirmed through an independent radiological review. However, the increase in the primary endpoint of overall survival by 2 months was not significant (HR = 0.91). A high proportion of patients (approximately 63% IFN/placebo; 55% Avastin/IFN) received a variety of non-specified, post-protocol anticancer therapies, including antineoplastic agents, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 16.

Table 16 Efficacy Results from Study BO17705

	BO17705	
	IFN + placebo	**IFN □ Avastin**
Number of patients	322	327
Progression-free survival		
Median (months)	5.4	10.2
Hazard ratio [95% CI]	0.63 [0.52; 0.75] (p-value □ 0.0001)	
Objective response rate (%) in patients with measurable disease		
N	289	306
Response rate	12.8%	31.4%
	(p-value □□□□□□□□)	
Overall survival		
Median (months)	21.3	23.3
Hazard ratio [95% CI]	0.91 [0.76; 1.10] (p-value 0.3360)	

An exploratory multivariate Cox regression model using backward selection indicated that the following baseline prognostic factors were strongly associated with survival independent of treatment: gender, white blood cell count, platelets, body-weight loss in the 6 months prior to study entry, number of metastatic sites, sum of longest diameter of target lesions, Motzer score. Adjustment for these baseline factors resulted in a treatment hazard ratio of 0.78 (95% CI [0.63; 0.96], p = 0.0219), indicating a 22% reduction in the risk of death for patients in the Avastin + IFN alfa-2a arm compared to the IFN alfa-2a arm.

Ninety-seven patients in the IFN alfa-2a arm and 131 patients in the Avastin arm reduced the dose of IFN alfa-2a from 9 MIU to either 6 or 3 MIU, three times a week as prespecified in the protocol. Dose reduction of IFN alfa-2a did not appear to affect the efficacy of the combination of Avastin and IFN alfa-2a, based on PFS event-free rates over time, as shown by a subgroup analysis. The 131 patients in the Avastin + IFN alfa-2a arm who reduced and maintained the IFN alfa-2a dose at 6 or 3 MIU during the study, exhibited at 6, 12 and 18 months PFS event-free rates of 73, 52 and 21% respectively, as compared to 61, 43 and 17% in the total population of patients receiving Avastin + IFN alfa-2a.

AVF2938

This was a randomised, double-blind, phase II clinical study investigating Avastin 10 mg/kg in a 2-weekly schedule with the same dose of Avastin in combination with 150 mg daily erlotinib in patients with metastatic clear-cell RCC. A total of 104 patients were randomised to treatment in this study, 53 to Avastin 10 mg/kg q2w + placebo and 51 to Avastin 10 mg/kg q2w + erlotinib 150 mg daily. The analysis of the primary endpoint showed no difference between the Avastin + placebo arm and the Avastin + erlotinib arm (median PFS 8.5 versus 9.9 months). Seven patients in each arm had an objective response.

Malignant Glioma (WHO Grade IV) – Glioblastoma

AVF3708g

The efficacy and safety of Avastin as treatment for patients with glioblastoma was studied in an open-label, multicentre, randomised, non-comparative study (AVF3708g).

Glioblastoma patients in first or second relapse after prior radiotherapy (completed at least 8 weeks prior to receiving Avastin) and temozolomide were randomised (1:1) to receive Avastin (10 mg/kg i.v. infusion every 2 weeks) or Avastin + irinotecan (125 mg/m^2 i.v. or 340 mg/m^2 i.v. for patients on enzyme-inducing antiepileptic drugs every 2 weeks) until disease progression or until unacceptable toxicity. The primary endpoints of the study were 6-month progression-free survival (PFS) and objective response rate (ORR) as assessed by an independent review facility (IRF). Other outcome measures were duration of PFS, duration of response and overall survival.

Results of the study are summarised in Table 17.

Table 17 Efficacy Results from Study AVF3708g

	Avastin		**Avastin + irinotecan**	
Number of patients	85		82	
	Inv	IRF	Inv	IRF

Primary endpoints				
6-month progression-free survival 95% CI (Inv) 97.5% CI (IRF)	43.6% (33.0, 54.3) -	42.6% - (29.6, 55.5)	57.9% (46.6, 69.2) -	50.3% - (36.8, 63.9)
Objective response rate 95% CI (Inv) 97.5% CI (IRF)	41.2% (30.6, 52.3) -	28.2% - (18.5, 40.3)	51.2% (39.9, 62.4) -	37.8% - (26.5, 50.8)
Secondary endpoints				
Progression-free survival (months) Median (95% CI)	4.2 (3.0, 6.9)	4.2 (2.9, 5.8)	6.8 (5.0, 8.2)	5.6 (4.4, 6.2)
Duration of objective response (months) Median (95% CI)	8.1 (5.5, *)	5.6 (3.0, 5.8)	8.3 (5.5, *)	4.3 (4.2, *)
Overall survival (months) Median (95% CI)	9.3 (8.2, *)		8.8 (7.8, *)	

ORR was determined using modified McDonald criteria; Inv = Investigator's assessment; IRF = Independent review facility
* Upper limit of the confidence interval could not be obtained

In study AVF3708g, 6-month PFS based on IRF assessments was significantly higher ($p < 0.0001$) compared with historical controls for both treatment arms: 42.6% in the Avastin arm and 50.3% in the Avastin + irinotecan arm (investigator assessment: 43.6% in the Avastin arm and 57.9% in the Avastin + irinotecan arm). Objective response rates were also significantly higher ($p < 0.0001$) compared with historical controls for both treatment arms: 28.2% in the Avastin arm and 37.8% in the Avastin + irinotecan arm (investigator assessment: 41.2% in the Avastin arm and 51.2% in the Avastin + irinotecan arm).

The majority of patients who were receiving steroids at baseline, including responders and non-responders, were able to reduce their steroid utilisation over time while receiving bevacizumab treatment. The majority of patients experiencing an objective response or prolonged PFS (at week 24) were able to maintain or improve their neurocognitive functions while on study treatment compared to baseline. The majority of patients that remained in the study and were progression-free at 24 weeks had a Karnofsky performance status (KPS) that remained stable.

BO21990

The efficacy and safety of Avastin in combination with temozolomide and radiotherapy as a treatment for patients with newly diagnosed glioblastoma, was studied in this randomised, 2 arm, double-blind, placebo-controlled, multicentre Phase III trial.

Patients with newly diagnosed supratentorial glioblastoma (GBM) were randomised to receive either Avastin (10 mg/kg IV infusion given once every 2 weeks) or placebo, concomitantly with 6

weeks of radiotherapy (total dose 60 Gy, administered as 2 Gy fractions, 5 days/week) and temozolomide (75 mg/m^2/day).

Then, following a 4 week treatment break, up to 6 cycles of temozolomide were administered (150 to 200 mg/m^2/day, day 1-5 of each 4 week cycle), along with Avastin (10 mg/kg IV infusion given once every 2 weeks) or placebo.

After treatment with combined Avastin and temozolomide; Avastin (15 mg/kg of body weight given once every 3 weeks), or placebo, was continued as a single agent, until disease progression or unacceptable toxicity.

Progression-free survival (PFS - as assessed by the investigator - Inv) and overall survival (OS) were defined as co-primary endpoints. The trial was designed to meet its primary objective if either of the co-primary endpoints met statistical significance. Secondary efficacy endpoints were PFS (as assessed by an independent review facility - IRF), 1-year and 2-year survival rates and health-related quality of life (HRQoL).

Results from the time of the final PFS and final OS analyses of the study are summarized in table 18.

Table 18 Efficacy Results from Study BO21990

	Placebo + Radiotherapy / Temozolomide N=463	**Avastin + Radiotherapy / Temozolomide N=458**
Primary End Points		
Progression-free survival (Inv) (KM-estimated median - months)	6.2	10.6
Hazard ratio (95% CI)[a]	0.64 (0.55; 0.74) (p-value[b] < 0.0001)	
Overall Survival (OS)[c] (KM-estimated median - months)	16.7	16.8
Hazard ratio (95% CI)[a]	0.88 (0.76; 1.02) (p-value[b]= 0.0987)	
Secondary End Points		
Progression-free survival (IRF) (KM-estimated median - months)	4.3	8.4
Hazard ratio (95% CI)[a]	0.61 (0.53; 0.71) (p-value[b] < 0.0001)	
Survival rates – (KM-estimated)		
1-year [c,d]	66% (62; 71)	72% (68; 77)
	(p-value[e] = 0.049)	
2-year [c,d]	30% (26; 34)	34% (29; 38)
	(p-value[e] = 0.235)	
HRQoL - Global Health Status (KM estimated median – months)[f]	3.9	6.4

- PD included as an event		
Hazard ratio (95% CI)	0.64 (0.56; 0.74) (p-value[b] < 0.0001)	
HRQoL - Global Health Status (KM estimated median – months) [f] - PD excluded as an event	5.6	8.5
Hazard ratio (95% CI)	0.76 (0.63; 0.92) (p-value[b] 0.0041)	
HRQoL Global Health Status – Progression-free time (Inv) stable or improved compared to baseline	67% of patients stable / improved [g] median duration 4 months	77% of patients stable / improved [g] median duration 8 months

[a]Treatment effect: compared to Pl+RT/T arm: for time to event parameters, estimates were calculated by
stratified Cox regression
[b] Log-Rank p value (stratified)
[c] Final OS analysis
[d] KM estimate and 95% CI
[e] p value from a Z-test
[f] time until definitive deterioration from baseline
[g] For at least one visit.
KM = Kaplan-Meier methodology

Study BO21990 demonstrated a statistically significant (p-value < 0.0001) 36% reduction in the risk of investigator-assessed progression or death (PFS) in the Avastin arm, compared to the placebo arm. The final OS analysis was not statistically significant (HR=0.88, p=0.0987)

The majority of deaths were due to progressive disease. Deaths from causes other than disease progression were reported in a similar proportion of patients in each arm: 32 [7.1 %] in the Placebo + Radiotherapy + Temozolomide arm (Pl+RT/T) and 30 [6.5 %] in the Bevacizumab + Radiotherapy + Temozolomide arm (Bv+RT/T). More of these non-progressive disease deaths were recorded as adverse events that led to death in the Avastin arm (20 [4.3%]) compared to the placebo arm (12 [2.7%]).

Overall, health-related quality of life (HRQoL) and clinical benefit results consistently indicated benefit in favour of the Avastin arm.

Patients treated with Avastin maintained their HRQoL during the progression-free time (median PFS 10.6 months) and had a longer time to definitive deterioration (defined as the time from randomization until HRQoL deterioration, disease progression or death) in global health status, physical functioning and social functioning measured using the EORTC QLQ-C30 questionnaire, and communication deficit and motor dysfunction measured using the EORTC QLQ-BN20 questionnaire compared to the control arm.

During the progression-free time, patients maintained their ability for independent self-care as measured by Karnofsky performance status ≥70.

Moreover, there was a diminished corticosteroid requirement in patients treated with Avastin.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Front-line Ovarian Cancer

The safety and efficacy of Avastin in the front-line treatment of patients with epithelial ovarian, fallopian tube or primary peritoneal cancer were studied in two phase III trials (GOG-0218 and BO17707) which compared the effect of the addition of Avastin to carboplatin and paclitaxel compared to the chemotherapy regimen alone.

GOG-0218

The GOG-0218 study was a phase III multicentre, randomised, double-blind, placebo-controlled, 3-arm study evaluating the effect of adding Avastin to an approved chemotherapy regimen (carboplatin and paclitaxel) in patients with optimally or sub-optimally debulked Stage III or Stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer.

A total of 1873 patients were randomised in equal proportions to the following three arms:

- CPP arm: Placebo in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy
- CPB15 arm: Five cycles of Avastin (15 mg/kg q3w) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles (Avastin commenced at cycle 2 of chemotherapy) followed by placebo alone, for a total of up to 15 months of therapy
- CPB15+ arm: Five cycles of Avastin (15 mg/kg q3w) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles (Avastin commenced at cycle 2 of chemotherapy) followed by continued use of Avastin (15 mg/kg q3w) as single agent for a total of up to 15 months of therapy.

The primary endpoint was Progression Free Survival (PFS) based on investigator's assessment of radiological scans. In addition, an independent review of the primary endpoint was also conducted.

The results of this study are summarised in Table 19.

Table 19 Efficacy Results from Study GOG-0218

Progression-free survival						
	Investigator Assessment[1]			**IRC Assessment**		
	CPP (n=625)	**CPB15 (n=1248)[2]**	**CPB15+ (n=1248)[2]**	**CPP (n=625)**	**CPB15 (n=1248)[2]**	**CPB15+ (n=1248)[2]**
Median PFS (months)	12.0	12.7	18.2	13.1	13.2	19.1
Hazard ratio (95% CI)[3]		0.842 [0.714, 0.993]	0.644 [0.541, 0.766]		0.941 [0.779, 1.138]	0.630 [0.513, 0.773]
p-Value[4]		0.0204[5]	< 0.0001[5]		0.2663	< 0.0001
Objective response rate[6]						

	Investigator Assessment			IRC Assessment		
	CPP (n=396)	**CPB15 (n=393)**	**CPB15+ (n=403)**	**CPP (n=474)**	**CPB15 (n=460)**	**CPB15+ (n=499)**
% pts with objective response	63.4	66.2	66.0	68.8	75.4	77.4
p-Value[3]		0.2341	0.2041		0.0106	0.0012

Overall survival[7]

	CPP (n=625)	**CPB15 (n=625)**[2]	**CPB15+ (n=623)**[2]
Median OS (months)	40.6	38.8	43.8
Hazard ratio (95% CI)[3]		1.065 (0.908, 1.249)	0.879 (0.745, 1.038)
p-Value[4]		0.2197	0.0641

[1] Primary PFS analysis
[2] Events prior to cycle 7 from the CPB15 and CPB15+ arms were pooled for the analyses
[3] Relative to the control arm; stratified hazard ratio
[4] One-sided log-rank p-value
[5] Subject to a p-value boundary of 0.0116
[6] Patients with measurable disease at baseline
[7] Final overall survival analysis

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone, patients who received front-line bevacizumab at a dose of 15 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab alone, had a clinically meaningful and statistically significant improvement in PFS.

Although there was an improvement in PFS for patients who received front-line bevacizumab in combination with chemotherapy and did not continue to receive bevacizumab alone, the improvement was neither clinically meaningful nor statistically significant compared to patients who received chemotherapy alone.

BO17707 (ICON7)

BO17707 was a phase III, two-arm, multicentre, randomised, controlled, open-label study comparing the effects of adding Avastin to carboplatin plus paclitaxel in patients with FIGO Stage I or IIA (Grade 3 or clear-cell histology only), or FIGO Stage IIB - IV (all grades and all histological types) epithelial ovarian, fallopian tube or primary peritoneal cancer following surgery, and in whom no further surgery was planned before progression.

A total of 1528 patients were randomised in equal proportions to the following two arms:

- CP arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles
- CPB7.5+ arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles plus Avastin (7.5 mg/kg q3w) for up to 18 cycles.

The primary endpoint was Progression Free Survival (PFS) as assessed by the investigator.

The results of this study are summarised in Table 20.

Table 20 Efficacy Results from Study BO17707 (ICON7)

Progression-free survival		
	CP (n= 764)	**CPB7.5+ (n=764)**
Median PFS (months)	16.0	18.3
Hazard ratio [95% CI]	0.79 [0.68; 0.91] (p-value = 0.0010)	
Objective Response Rate[1]		
	CP (n=277)	**CPB7.5+ (n=272)**
Response rate	41.9%	61.8%
	(p-value <0.0001)	
Overall Survival[2]		
	CP (n= 764)	**CPB7.5+ (n=764)**
Median (months)	58.0	57.4
Hazard ratio [95% CI]	0.99 [0.85; 1.15]	

[1] In patients with measurable disease at baseline
[2] Final OS analysis when 46.7% of patients died

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone, patients who received bevacizumab at a dose of 7.5 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab for up to 18 cycles had a statistically significant improvement in PFS.

Recurrent Ovarian Cancer

GOG-0213

GOG-0213 was a phase III randomized controlled trial studying the safety and efficacy of Avastin in the treatment of patients with platinum-sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who have not received prior chemotherapy in the recurrent setting. There was no exclusion criterion for prior anti-angiogenic therapy. The study evaluated the effect of adding Avastin to carboplatin+paclitaxel and continuing Avastin as a single agent compared to carboplatin+paclitaxel alone.

A total of 673 patients were randomized in equal proportions to the following two treatment arms.

- CP arm: Carboplatin (AUC5) and paclitaxel (175 mg/m^2 IV over 3 hours) every 3 weeks for 6 and up to 8 cycles.
- CPB arm: Carboplatin (AUC5) and paclitaxel (175 mg/m^2 IV over 3 hours) and concurrent Avastin (15 mg/kg) every 3 weeks for 6 and up to 8 cycles followed by Avastin (15 mg/kg every 3 weeks) alone until disease progression or unacceptable toxicity.

The primary efficacy endpoint was overall survival (OS). The main secondary efficacy endpoint was progression-free survival (PFS). Objective response rates (ORR) were also examined. Results are presented in Table 21.

Table 21 Efficacy results from study GOG-0213

Primary Endpoint		
Overall Survival (OS)	CP (n=336)	CPB (n=337)
Median OS (months)	37.3	42.6
Hazard ratio [95% CI]	0.823 (CI: 0.680, 0.996)	
p-Value	0.0447	
Secondary Endpoints		
Progression-free survival (PFS)	CP (n=336)	CPB (n=337)
Median PFS (months)	10.2	13.8
Hazard ratio [95% CI]	0.613 (CI: 0.521, 0.721)	
p-value	<0.0001	
Objective response rate	CP* (n=286)	CPB* (n=274)
No. (%) of pts with objective response (CR, PR)	159 (55.6%)	213 (77.7%)
p –value	<0.0001	

*Intent-to-treat population with measureable disease at baseline

Treatment with Avastin at 15 mg/kg every 3 weeks in combination with chemotherapy (carboplatin and paclitaxel) for 6 and up to 8 cycles then followed by Avastin as a single agent resulted in a clinically meaningful and statistically significant improvement in OS compared to treatment with carboplatin and paclitaxel alone.

AVF4095g

The safety and efficacy of Avastin in the treatment of patients with platinum-sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior chemotherapy in the recurrent setting or prior bevacizumab treatment was studied in a phase III trial randomised, double-blind, placebo-controlled trial (AVF4095g). The study compared the effect of adding Avastin to and carboplatin and gemcitabine chemotherapy, and continuing Avastin as a single agent to progression to carboplatin and gemcitabine alone.

A total of 484 patients with measurable disease were randomised in equal proportions to either:

- Carboplatin (AUC 4, day 1) and gemcitabine (1000 mg/m^2 on days 1 and 8) and concurrent placebo every 3 weeks for 6 and up to 10 cycles followed by placebo alone until disease progression or unacceptable toxicity
- Carboplatin (AUC 4, day 1) and gemcitabine (1000 mg/m^2 on days 1 and 8) and concurrent Avastin (15 mg/kg day 1) every 3 weeks for 6 and up to 10 cycles followed by Avastin (15 mg/kg every 3 weeks) alone until disease progression or unacceptable toxicity.

The primary endpoint was progression-free survival based on investigator assessment using RECIST criteria. Additional endpoints included objective response, duration of response, safety and overall survival. An independent review of the primary endpoint was also conducted.

The results of this study are summarised in Table 22.

Table 22 Efficacy Results from Study AVF4095g

Progression-free survival				
	Investigator Assessment*		**IRC Assessment**	
	Placebo+ C/G (n = 242)	**Avastin + C/G (n = 242)**	**Placebo+ C/G (n = 242)**	**Avastin + C/G (n = 242)**
Median PFS (months)	8.4	12.4	8.6	12.3
Hazard ratio (95% CI)	0.484 [0.388; 0.605]		0.451 [0.351; 0.580]	
p-Value	<0.0001		<0.0001	
Objective response rate				
	Investigator Assessment		IRC Assessment	
	Placebo+ C/G (n = 242)	**Avastin + C/G (n = 242)**	**Placebo+ C/G (n = 242)**	**Avastin + C/G (n = 242)**
% pts with objective response	57.4%	78.5%	53.7%	74.8%
p-Value	<0.0001		<0.0001	
Overall survival**				
	Placebo + C/G (n = 242)		**Avastin + C/G (n = 242)**	
Median OS (months)	32.9		33.6	
Hazard ratio (95% CI)	0.952 [0.771; 1.176]			
p-Value	0.6479			

* Primary analysis

** Final overall survival analysis performed when approximately 73% of the patients had died

MO22224 (AURELIA)

Study MO22224 evaluated the efficacy and safety of bevacizumab in combination with chemotherapy for platinum-resistant recurrent ovarian cancer. This study was designed as an open-label, randomised, two-arm phase III evaluation of bevacizumab plus chemotherapy (CT+BV) versus chemotherapy alone (CT).

A total of 361 patients were enrolled into this study and administered either chemotherapy (paclitaxel, topotecan, or PLD) alone or in combination with bevacizumab:

- CT arm (chemotherapy alone):
  - Paclitaxel 80 mg/m^2 as a 1-hour i.v. infusion on days 1, 8, 15, and 22 every 4 weeks.
  - Topotecan 4 mg/m^2 as a 30-minute i.v. infusion on days 1, 8, and 15 every 4 weeks. Alternatively, a 1.25 mg/m^2 dose could be administered over 30 minutes on days 1–5 every 3 weeks.
  - PLD 40 mg/m^2 as a 1-mg/min i.v. infusion on day 1 only every 4 weeks. After cycle 1, the drug could be delivered as a 1-hour infusion.

- CT+BV arm (chemotherapy plus bevacizumab):
  - The chosen chemotherapy was combined with bevacizumab 10 mg/kg i.v. every 2 weeks (or bevacizumab 15 mg/kg every 3 weeks if used in combination with topotecan 1.25 mg/m^2 on days 1–5 on an every 3-week schedule).

Eligible patients had ovarian cancer that progressed within 6 months of previous platinum therapy. If a patient had been previously included in a blinded trial with an anti-angiogenic agent, the patient was enrolled in the same stratum as those patients who were known to have previously received an anti-angiogenic agent.

The primary endpoint was progression-free survival, with secondary endpoints including objective response rate and overall survival. Results are presented in Table 23.

Table 23 Efficacy Results from Study MO22224 (AURELIA)

Primary Endpoint		
Progression-Free Survival		
	CT (n=182)	**CT+BV (n=179)**
Median (months)	3.4	6.7
Hazard ratio (95% CI)	0.379 [0.296; 0.485]	
p-Value	<0.0001	
Secondary Endpoints		
Objective Response Rate*		
	CT (n=144)	**CT+BV (n=142)**
% pts with objective response	18 (12.5%)	40 (28.2%)
p-Value	0.0007	
Overall Survival (final analysis)**		
	CT (n=182)	**CT+BV (n=179)**
Median OS (months)	13.3	16.6
Hazard ratio (95% CI)	0.870 [0.678; 1.116]	

p-Value	0.2711

All analyses presented in this table are stratified analyses
* Randomised patients with measurable disease at baseline
**At the time of the final OS analysis (25 January 2013), 266 patients (73.3%) had died across the two treatment arms.

Cervical Cancer

GOG-0240

The efficacy and safety of bevacizumab in combination with chemotherapy (paclitaxel and cisplatin or paclitaxel and topotecan) as a treatment for patients with persistent, recurrent, or metastatic carcinoma of the cervix was evaluated in study GOG-0240, a randomised, four-arm, multi-centre phase III trial.

A total of 452 patients were randomised to receive either:

- Paclitaxel 135 mg/m^2 i.v. over 24 hours on day 1 and cisplatin 50 mg/m^2 i.v. on day 2, every 3 weeks (q3w); or paclitaxel 175 mg/m^2 i.v. over 3 hours on day 1 and cisplatin 50 mg/m^2 i.v. on day 2 (q3w); or paclitaxel 175 mg/m^2 i.v. over 3 hours on day 1 and cisplatin 50 mg/m^2 i.v. on day 1 (q3w)
- Paclitaxel 135 mg/m^2 i.v. over 24 hours on day 1 and cisplatin 50 mg/m^2 i.v. on day 2 plus bevacizumab 15 mg/kg i.v. on day 2 (q3w); or paclitaxel 175 mg/m^2 i.v. over 3 hours on day 1 and cisplatin 50 mg/m^2 i.v. on day 2 plus bevacizumab 15 mg/kg i.v. on day 2 (q3w); or paclitaxel 175 mg/m^2 i.v. over 3 hours on day 1 and cisplatin 50 mg/m^2 i.v. on day 1 and bevacizumab 15 mg/kg i.v. on day 1 (q3w)
- Paclitaxel 175 mg/m^2 over 3 hours on day 1 and topotecan 0.75 mg/m^2 over 30 minutes on days 1–3 (q3w)
- Paclitaxel 175 mg/m^2 over 3 hours on day 1 and topotecan 0.75 mg/m^2 over 30 minutes on days 1–3 plus bevacizumab 15 mg/kg i.v. on Day 1 (q3w).

Eligible patients had persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which was not amenable to curative treatment with surgery and/or radiation therapy.

The primary efficacy endpoint was overall survival (OS). Secondary efficacy endpoints included progression-free survival (PFS) and objective response rate (ORR). Results are presented in Table 24.

Table 24 Overall Efficacy of Bevacizumab Treatment (ITT Population) from Study GOG-0240

	Chemotherapy (n=225)	Chemotherapy + BV (n=227)
Primary Endpoint		
Overall Survival		
Median (months)[1]	12.9	16.8
Hazard ratio [95% CI]	0.74 [0.58; 0.94] (p-value[5] = 0.0132)	
Secondary Endpoints		
Progression-free survival		
Median PFS (months)[1]	6.0	8.3
Hazard ratio [95% CI]	0.66 [0.54; 0.81] (p-value[5] = <0.0001)	
Best Overall Response		
Response rate[2]	76 (33.8%)	103 (45.4%)
95% CI for response rates[3]	[27.6; 40.4]	[38.8; 52.1]
Difference in response rates	11.60	
95% CI for difference in response rates[4]	[2.4; 20.8]	
p-Value (Chi-squared test)	0.0117	

[1] Kaplan-Meier estimates
[2] Patients with best overall response of confirmed CR or PR
[3] 95% CI for one sample binomial using the Pearson-Clopper method
[4] Approximate 95% CI for difference of two rates using the Hauck-Anderson method
[5] Log-rank test (stratified)

3.1.3 Immunogenicity

No robust assessment of anti-drug antibodies has been done in Avastin clinical trials.

3.2 Pharmacokinetic Properties

The pharmacokinetics of bevacizumab were characterised in patients with various types of solid tumours. The doses tested were 0.1-10 mg/kg weekly in phase I; 3-20 mg/kg every 2 weeks (q2w) or every 3 weeks (q3w) in phase II; 5 mg/kg (q2w) or 15 mg/kg (q3w) in phase III. In all clinical trials, bevacizumab was administered as an i.v. infusion.

As observed with other antibodies, the pharmacokinetics of bevacizumab are well described by a two-compartmental model. Overall, in all clinical trials, bevacizumab disposition was characterised by a low clearance, a limited volume of the central compartment (V_c), and a long elimination half-life. This enables target therapeutic bevacizumab plasma levels to be maintained with a range of administration schedules (such as one administration every 2 or 3 weeks).

In the population pharmacokinetic analysis there was no significant difference in the pharmacokinetics of bevacizumab in relation to age (no correlation between bevacizumab clearance and patient age [the median age was 59 years with 5th and 95th percentiles of 37 and 76 years]).

Low albumin and high tumour burden are generally indicative of disease severity. Bevacizumab clearance was approximately 30% faster in patients with low levels of serum albumin and 7% faster in subjects with higher tumour burden when compared with a typical patient with median values of albumin and tumour burden.

3.2.1 Distribution

The typical value for central volume (V_c) was 2.73 l and 3.28 l for female and male subjects, respectively, which is in the range that has been described for IgGs and other monoclonal antibodies. The typical value for peripheral volume (V_p) was 1.69 l and 2.35 l for female and male patients, respectively, when bevacizumab is co-administered with antineoplastic agents. After correcting for body weight, male subjects had a larger V_c (+ 20%) than females.

3.2.2 Metabolism

Assessment of bevacizumab metabolism in rabbits following a single i.v. dose of ^{125}I-bevacizumab indicated that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF. The metabolism and elimination of bevacizumab are similar to those of endogenous IgG, i.e. primarily via proteolytic catabolism throughout the body including endothelial cells, and do not rely primarily on elimination through the kidneys and liver. Binding of the IgG to the FcRn receptor results in protection from cellular metabolism and a long terminal half-life.

3.2.3 Elimination

The pharmacokinetics of bevacizumab are linear at doses ranging from 1.5 to 10 mg/kg/week.

The value for clearance is, on average, equal to 0.188 and 0.220 l/day for female and male patients, respectively. After correcting for body weight, male patients had a higher bevacizumab clearance (+ 17%) than females. According to the two-compartmental model, the elimination half-life is 18 days for a typical female patient and 20 days for a typical male patient.

3.2.4 Pharmacokinetics in Special Populations

The population pharmacokinetics of bevacizumab were analysed to evaluate the effects of demographic characteristics. In adults, the results showed no significant difference in the pharmacokinetics of bevacizumab in relation to age.

Pediatric Population: The pharmacokinetics of bevacizumab were evaluated in 152 patients (7 months to 21 years; 5.9 to 125kg) across 4 clinical studies using a population pharmacokinetic model. The pharmacokinetic results show that the clearance and the volume of distribution of bevacizumab were comparable between pediatric and adult patients when normalized by body-weight. Age was not associated with the pharmacokinetics of bevacizumab when body-weight was taken into account.

Renal impairment: No studies have been conducted to investigate the pharmacokinetics of bevacizumab in renally impaired patients since the kidneys are not a major organ for bevacizumab metabolism or excretion.

Hepatic impairment: No studies have been conducted to investigate the pharmacokinetics of bevacizumab in patients with hepatic impairment since the liver is not a major organ for bevacizumab metabolism or excretion.

3.3 Nonclinical Safety

3.3.1 Carcinogenicity

Studies have not been performed to evaluate the carcinogenic potential of Avastin.

3.3.2 Genotoxicity

Studies have not been performed to evaluate the mutagenic potential of Avastin.

3.3.3 Impairment of Fertility

No specific studies in animals have been performed to evaluate the effect of Avastin on fertility. No adverse effect on male reproductive organs was observed in repeat-dose toxicity studies in cynomolgus monkeys.

Inhibition of ovarian function was characterised by decreases in ovarian and/or uterine weight and the number of corpora lutea, a reduction in endometrial proliferation and an inhibition of follicular maturation in cynomolgus monkeys treated with Avastin for 13 or 26 weeks. The doses associated with this effect were □□4 times the human therapeutic dose or ≥ 2-fold above the expected human exposure based on average serum concentrations in female monkeys. In rabbits, administration of 50 mg/kg of Avastin resulted in a significant decrease in ovarian weight and number of corpora lutea. The results in both monkeys and rabbits were reversible upon cessation of treatment. The inhibition of angiogenesis following administration of Avastin is likely to result in an adverse effect on female fertility.

3.3.4 Reproductive Toxicity

Avastin has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in maternal and foetal body weights, an increased number of foetal resorptions and an increased incidence of specific gross and skeletal foetal alterations. Adverse foetal outcomes were observed at all tested doses of 10–100 mg/kg. Information on foetal malformations observed in the post-marketing setting are provided in sections 2.5.1 Pregnancy (2.5 Use in Special Populations) and 2.6.2 Postmarketing Experience (2.6 Undesirable Effects).

3.3.5 Other

Physeal Development:

In studies of up to 26 weeks duration in cynomolgus monkeys, Avastin was associated with physeal dysplasia. Physeal dysplasia was characterised primarily by thickened growth plate cartilage, subchondral bony plate formation and inhibition of vascular invasion of the growth plate. This effect occurred at doses ≥ 0.8 times the human therapeutic dose and exposure levels

slightly below the expected human clinical exposure, based on average serum concentrations. It should be noted, however, that physeal dysplasia occurred only in actively growing animals with open growth plates.

Wound Healing:

In rabbits, the effects of Avastin on circular wound healing were studied. Wound re-epithelialisation was delayed in rabbits following five doses of Avastin ranging from 2 to 50 mg/kg, over a 2-week period. A trend toward a dose-dependent relationship was observed. The magnitude of effect on wound healing was similar to that observed with corticosteroid administration. Upon treatment cessation with either 2 or 10 mg/kg Avastin, the wounds closed completely. The lower dose of 2 mg/kg was approximately equivalent to the proposed clinical dose. A more sensitive linear wound-healing model was also studied in rabbits. Three doses of Avastin ranging from 0.5 to 2 mg/kg dose-dependently and significantly decreased the tensile strength of the wounds, consistently with delayed wound healing. The low dose of 0.5 mg/kg was 5-fold below the proposed clinical dose.

As effects on wound healing were observed in rabbits at doses below the proposed clinical dose, the capacity for Avastin to adversely impact wound healing in humans should be considered.

In cynomolgus monkeys, the effects of Avastin on the healing of a linear incision were highly variable and no dose-response relationship was evident.

Renal Function:

In normal cynomolgus monkeys, Avastin had no measurable effect on renal function treated once or twice weekly for up to 26 weeks, and did not accumulate in the kidney of rabbits following two doses of up to 100 mg/kg (approximately 80-fold the proposed clinical dose).

Investigative toxicity studies in rabbits, using models of renal dysfunction, showed that Avastin did not exacerbate renal glomerular injury induced by bovine serum albumin or renal tubular damage induced by cisplatin.

Albumin:

In male cynomolgus monkeys, Avastin administered at doses of 10 mg/kg twice weekly or 50 mg/kg once weekly for 26 weeks was associated with a statistically significant decrease in albumin and albumin to globulin ratio and increase in globulin. These effects were reversible upon cessation of exposure. As the parameters remained within the normal reference range of values for these endpoints, these changes were not considered as clinically significant.

Hypertension:

At doses up to 50 mg/kg twice weekly in cynomolgus monkeys, Avastin showed no effects on blood pressure.

Haemostasis:

Non-clinical toxicology studies of up to 26 weeks duration in cynomolgus monkeys did not find changes in haematology or coagulation parameters including platelet counts, prothrombin and activated partial thromboplastin time. A model of haemostasis in rabbits, used to investigate the

effect of Avastin on thrombus formation, did not show alteration in the rate of clot formation or any other haematological parameters compared to treatment with Avastin vehicle.

4. PHARMACEUTICAL PARTICULARS

4.1 List of Excipients

Trehalose dihydrate, sodium phosphate, polysorbate, water for injections.

4.2 Storage

Avastin should not be used after the expiry date (EXP) shown on the pack.

Store vials in a refrigerator at 2°C-8°C.

Keep vial in the outer carton in order to protect from light.

DO NOT FREEZE. DO NOT SHAKE.

Shelf-life of the solution for infusion containing the reconstituted product

Avastin does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

Chemical and physical in-use stability has been demonstrated for 30 days at 2°C-8°C plus an additional 48 hours at 2°C-30°C in 0.9% sodium chloride solution. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place under controlled and validated aseptic conditions.

4.3 Special Instructions for Use, Handling and Disposal

Avastin infusions should not be administered or mixed with dextrose or glucose solutions (see "Incompatibilities" below).

Do not administer as an i.v. push or bolus.

Avastin should be prepared by a healthcare professional using an aseptic technique. Use sterile needle and syringe to prepare Avastin. Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1.4 - 16.5 mg/ml.

Discard any unused portion left in the vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

Avastin is not formulated for intravitreal use.

Incompatibilities

No incompatibilities between Avastin and polyvinyl chloride or polyolefin bags have been observed. A concentration-dependent degradation profile of Avastin was observed when diluted with dextrose solutions (5%).

Disposal of unused/expired medicines

The release of pharmaceuticals into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

4.4 Packs

Vial 400 mg/16 ml	1
Vial 100 mg/4 ml	1

Medicine: keep out of reach of children

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